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THE BLOOD-CHOLESTEROL RESPONSE TO INTRAVENOUS THERAPY IN PERIPHERAL ARTERIAL DISEASE.

By Harry G. Jacobi, M.D.,

ASSOCIATE ATTENDING PHYSICIAN, LENOX HILL HOSPITAL, NEW YORK CITY.

(From the Medical Service of Dr. A. L. Garbat.)

Various therapeutic procedures have been advocated for the relief of symptoms due to peripheral vascular lesions. These have included such measures as the intravenous administration of hypertonic solutions, typhoid vaccine therapy and passive vascular exercises (Pavaex therapy). We have been particularly interested in the intravenous forms of therapy, and have been cognizant of the fact that their use in these cases has been based upon purely empirical data.

In 1934, I[1] reported the value of intravenous physiologic saline therapy in a case of polycythemia vera, with painful ulceration of the foot, due to peripheral arterial disease. Since that time we have employed solutions of sodium iodide as well as the chloride, in various concentrations, in similar cases of painful ulcerative lesions of the extremities due to peripheral arterial disease, with very satisfactory results.

During the period of treatment, our cases were carefully studied in order to determine whether any significant changes could be detected in the blood chemistry that might be of some diagnostic or therapeutic help. Certain striking and characteristic changes did occur in the blood cholesterol and it is these observations which constitute the basis of this communication.

Before entering upon the report of our observations, however, it might be well to review some well-established facts regarding the

chemical changes in peripheral vascular lesions, and the part played by such substances as cholesterol, chlorides, iodides and calcium in this disease process.

Arteriosclerosis and Calcification. As is well known, elastic tissue is particularly prone to early calcification, and it is not uncommon to see the elastic laminæ of the small arteries calcified in an apparently selective manner. The deposition of the calcium can only be explained on theoretical conclusions and such explanations must be accepted until more definite experimental data are obtained. Thus Lichtwitz[7] advanced the idea that precipitation of the colloids in areas of degeneration decreases the amount of the crystalloids which can be held in solution. As a result of this the least soluble salts, those of calcium, are precipitated. By the laws of osmotic pressure, more calcium will then enter to establish equilibrium, be precipitated, and make way for more calcium until the amount of the deposit prevents further osmotic diffusion. Wells[12] contends that the deposition of calcium salts in areas of tissue degeneration depends upon one or more of several factors, such as tissue reaction, protein content, and so on. In many of the cases of peripheral arterial disease that have come under our observation, the degree of calcification was quite marked and could very easily be demonstrated by roentgenograms.

Chlorides and Iodides in Relation to the Body Fluids. The work of Loeb, Atchley and Palmer[8] is of extreme interest in this connection. They found that edema fluid contains more chloride and less potassium than the blood serum, while the sodium, carbonic acid, calcium, urea, glucose and non-protein nitrogen exist in approximately the same concentrations in the serum as in the edema fluid. The reason for this variation in the chloride content of serum and edema fluid was found to be due to a difference in the concentration of the proteins of the two fluids. This effect was quite similar to that obtained in a simple membrane equilibrium. Van Slyke, Wu and McLean,[10] in an extensive study of the electrolyte and water distribution in the blood, have demonstrated the validity of the application of this purely physiochemical concept to the problems of equilibria in the blood and tissues. It might also be mentioned here that a similar phenomenon is noted in diabetic acidosis, where dehydration with considerable loss in blood chloride has been shown to occur and where the symptoms of dehydration clear up only after the administration of a definite amount of chlorides to the blood.

The rôle of iodine in the dissolution of necrotic and fibrotic material has also received considerable attention and has had ample clinical substantiation. Jobling and Peterson[5] were the first to offer a theoretical explanation for such action, particularly with respect to gumma formation. These investigators maintained that the softening and removal of necrotic fibrotic material depended normally upon the action of a tryptic ferment. In the case of the

gumma, for example, the lesion persists and remains firm because it contains large quantities of so-called antitryptic substances which are of lipoid nature, being combinations of unsaturated fatty acids. Whether these lipoid substances contained cholesterol was not determined at that time. Their power of antagonizing the normal tryptic ferment was found to depend upon their unsaturation, which in turn could be completely satisfied by iodine.

Cholesterol. Considerable detailed work has been published regarding the chemical and physiologic properties of this substance. Recent studies in the vitamin field, for example, suggests that cholesterol may have more active functions than had hitherto been appreciated.[3] It is our purpose, however, only to mention those facts which have a direct bearing on our present problem.

Cholesterol is an alcohol which may exist both free and in combination with fatty acids. It is the least soluble constituent of the red blood corpuscles' stroma and accumulates in extravasations as large thin plates. In various degenerative processes in the body, cholesterol is characteristically found in increased amounts. In endarteritis obliterans, various investigators[1] have reported finding an increased amount of cholesterol in the arterial walls. It has also been repeatedly observed that certain poisons like saponin failed to effect hemolysis in immunized animals, due to the increased amount of cholesterol present. The defensive mechanism of the animal to such toxins seems to be an increased mobilization of this substance in the blood, where it appears to bind and neutralize the poisons in much the same manner as the antitoxins neutralize toxins.[11] On the other hand, phagocytosis has been found to be definitely inhibited by cholesterol.[2] It is of further interest to note that in studying the sedimentation rate of the red blood corpuscles, Kurten[6] found that increased amounts of cholesterol are found to be present where the sedimentation rate is increased and that the addition of cholesterol to a specimen results in an increase in its sedimentation rate.

Procedure. The patients included in the present studies, all presented, at the time of admission, signs of peripheral arterial disease of the occluding type, associated with painful ulcerations of the extremities. The patients are kept at bed rest for the entire period of treatment, lasting from 4 to 6 weeks. Complete chemical blood and cholesterol determinations are made on admission. The cholesterol determinations are repeated about every 4 to 6 days. Intravenous therapy, consisting of 200 cc. of a 2% solution of sodium iodide in physiological salt solution is given every other day. Where idiosyncrasies or unusual systemic reactions are observed, indicative of iodine intolerance, a 2% sodium chloride solution is substituted. These solutions must be freshly prepared and do not require buffering. Solutions that are more than 24 hours old should be discarded as they have been found to produce severe and unpleasant systemic reactions. The local lesions are treated with dry heat and are properly protected from pressure and other possible traumatic injury. Where a diabetes coëxists, adequate dietary treatment with insulin, if necessary, is given.

Observations. The present report is based on 12 cases. Their ages vary from 41 to 73 years; 8 are males and 4 females. In 1 case the lesion was secondary to an embolus that had occurred postoperatively 10 years prior to the onset of the ulceration of the extremity; 3 had a complicating diabetes; 4 required more than one course of treatments. The entire group showed the same response as manifested by a cessation of the pain after receiving several of the intravenous treatments and complete healing of the ulcerative lesion at the end of the period of treatment. The shortest period during which the patient remained free from pain or recurrence of the ulceration after a single course of treatments is 2 months, while the longest period is 18 months, with an average period of 8 months for the entire group. The longest period of follow-up for the entire group, with freedom from pain or ulceration, is 5 years. The only significant changes noted in our blood chemical studies during the course of treatment relates to the blood cholesterol (Table 1) and these changes were shown by each case in the group.

Blood-cholesterol Response. The initial blood-cholesterol level of our patients with peripheral arterial disease, accompanied by pain and ulceration shows either a subnormal or low normal value. The lowest blood cholesterol in our series is 80 mg. per 100 cc. of blood serum. After several treatments with the chloride or iodide solutions, a sharp rise in the blood cholesterol is invariably noted, which is followed by a subsequent fall to the normal level as the treatment is continued. Table 1 shows the type of blood-cholesterol curve obtained during the course of treatment in these cases. In some of the cases in Table 1, the height of the cholesterol response amounted to almost 3 times that of the initial figure.

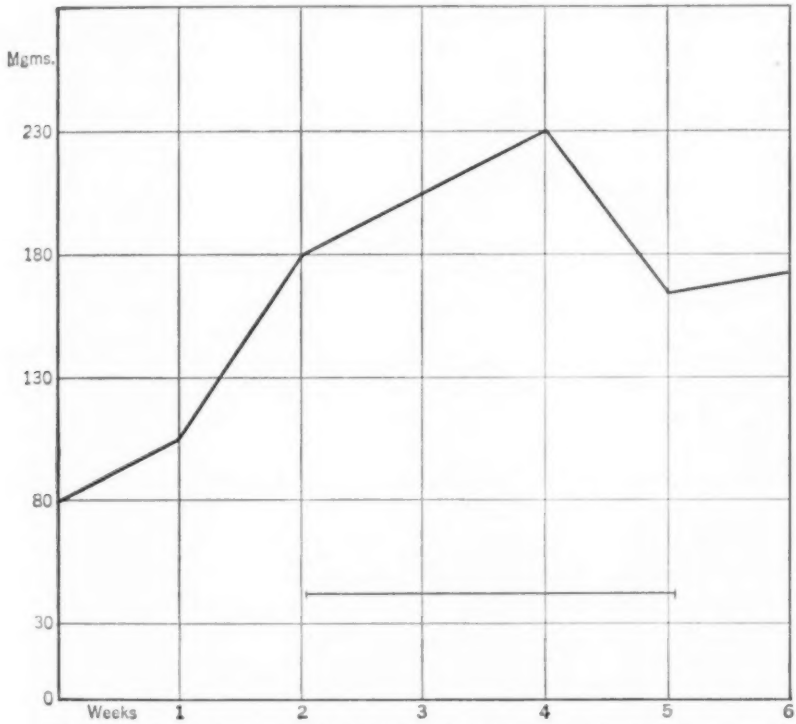
TABLE 1.—BLOOD CHOLESTEROL IN PERIPHERAL ARTERIAL DISEASE.

Case.	Age.	Sex.	Cholesterol determinations. 1st.	2d.	3d.	4th.	5th.	6th.	Blood cholesterol with recurrence.
R. A.	73	F	110	150	210	285	240	220	130 mg./100 cc.
A. S.	56	M	80	105	180	210	230	160	120 mg./100 cc.
J. E.	54	M	125	150	190	230	250	200	
S. K.	41	F	130	170	200	225	240	180	150 mg./100 cc.
E. T.	59	M	170	210	285	260	210	200	
M. T.	70	M	165	190	245	230	210	210	
L. W.	65	F	100	140	165	240	205	180	
O. S.	70	M	160	180	296	276	215	166	
F. K.	63	M	198	230	245	285	240	205	
H. H.	58	M	175	200	230	265	220	185	
T. F.	54	F	150	185	260	240	220	200	135 mg./100 cc.
B. G.	64	M	135	170	230	220	200	210	

Several significant observations, however, may be pointed out: (1) The fact that the initial blood cholesterol is either subnormal or normal. (2) The lower the initial blood cholesterol, the more rapid and more marked is the relief from pain and the healing process. (3) With the recurrence of the symptoms, the blood cholesterol is again found to be lowered, considerably below the level at the termination of the previous course of treatments. We

have noted that this decrease in the blood cholesterol occurs some time before the recurrence of the pain and ulceration. By making use of this finding, the patient may be spared a great deal of unnecessary pain and discomfort, by its employment as an indication for the institution of further treatment.

Discussion. In the small series of cases that we now have available, it is, of course, very difficult definitely to evaluate the findings. While no attempt can be made at present to interpret the



GRAPH 1.—Curve showing typical blood cholesterol response to intravenous treatment with chloride and iodide solutions.

results in terms of pathologic processes, it is interesting to attempt to fit in these observations with the available data and theoretical explanations that have been published regarding peripheral arterial disease.

As is well known, arteriosclerotic lesions, varying from slight thickening to a severe form of obliterating endarteritis, contain pathologic deposits of glycerine and cholesterol esters. These substances readily split up and become saponified, with the liberation of the soluble glycerine and crystalline cholesterol. Of the soaps formed with the resultant fatty acids, calcium soaps are

insoluble and remain where they are formed, until the advent of phosphates in the circulating blood causes another reaction to occur whereby the calcium becomes deposited in the form of hard calcium phosphates. The phosphoric acid in this reaction is supplied principally by the nucleoproteins and lecithins which usually undergo decomposition whenever tissue degeneration takes place. The source of the fatty acids is likewise not difficult to explain, as they are abundant in fatty degeneration processes which usually go on in areas of degeneration.

The deposition of the calcium salts in the wall of the arterial vessels thus continues, as the damage to the vessel wall increases. Cholesterol plays a very important rôle in this process. With the first signs of damage in the walls of the blood vessels, fatty degeneration with the resultant liberation of fatty acids soon takes place as part of the degenerative process. There is present in such lesions antitryptic substances[5] which have been described as having chemically the properties of unsaturated fatty acids. The first reaction to the above-described degenerative process is a demand upon the available supply of cholesterol as Nature's means of counteracting the fatty acid liberation, with the resultant formation of cholesterol esters. As the process becomes more generalized, a greater demand is made upon the available body cholesterol. This explanation is actually borne out by our findings of a low-cholesterol concentration in the circulating blood stream in most of our cases of peripheral arterial disease that have developed ulcerative lesions of the extremities. In 1 of our cases, this figure is found to be as low as 80 mg. In certain individuals, it would seem that the supply of available cholesterol in the body may be more abundant than in others and in such cases the value of the circulating blood cholesterol does not reach such a low level. Perhaps these are the cases that are more resistant to ulcerative and gangrenous manifestations. It would again appear, therefore, that a low blood cholesterol is not always a necessary finding in cases of generalized arteriosclerosis unless the particular individual is the type which will eventually develop ulcerative lesions. In such cases there appears to be a limited supply of available cholesterol. Coincident with the improvement in the ulcerative lesion, there occurs in all these cases a rise in the blood cholesterol and in the case cited above, where the blood cholesterol at the beginning of the treatment is 80 mg. per 100 cc. of blood, it rises to 230 mg. during the course of treatment. This constitutes practically a rise to 3 times that of the low level. On the other hand, with the recurrence of the symptoms in this particular case, a drop in the blood cholesterol is again noticed to 120 mg. per 100 cc. of blood serum. Another course of intravenous treatments is instituted followed by healing of the ulcerative lesion. The blood cholesterol again rises during the treatment period to 265 mg. in this particular case. This fluctuation in the

blood cholesterol, if properly employed, furnishes a guide, so to speak, as to the indication for resumption of intravenous therapy in a particular case.

It might also be mentioned at this point that the oral administration of these same iodide and chloride preparations was tried for a sufficiently long period of time in each case and proved completely ineffective in all of them. This failure can be explained as due in all probability to two chief reasons: (1) These preparations cannot be tolerated by the patient in sufficiently large doses and over a sufficiently long period of time necessary to have any effect upon the lesions. (2) The poor local circulatory condition present in these ulcerative lesions makes penetration of these preparations very indefinite and highly improbable when administered orally.

Conclusion. Patients with painful ulcerative lesions of the extremities due to peripheral arterial disease, should receive intravenous treatments with sodium iodide or sodium chloride solutions as described above, using the blood cholesterol as an important guide and indication in the administration of such therapy. It is hardly advisable, in the light of our observations, to await the recurrence of ulceration and pain in such cases and inasmuch as our average period of relief is about 8 months, that period of time might be the accepted interval at which time these periodic series of treatments might be instituted, unless indications exist for an earlier resumption of the therapy.

Summary. 1. Cases with painful ulcerative lesions of the extremities due to peripheral arterial disease, were found to have a subnormal or low normal blood cholesterol.

2. After intravenous treatment with 2% sodium iodide prepared in physiologic saline solution, cessation of pain was obtained in all cases.

3. Blood determinations made at repeated intervals during the course of treatment showed a gradual and marked rise in the blood cholesterol content with a subsequent fall.

4. The ulcerative lesions were healed after a period of treatments varying from 4 to 6 weeks.

5. With the recurrence of the peripheral ulcerative lesion a lowering in the blood-cholesterol value was again observed.

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THE HEMATOLOGIC PICTURE OF CHRONIC ULCERATIVE COLITIS; ITS RELATION TO PROGNOSIS AND TREATMENT.

By Robert O. Garvin, M.D.,*
ASSOCIATE, SERVICE ON GASTROENTEROLOGY, WESTERN PENNSYLVANIA AND ST. MARGARET MEMORIAL HOSPITALS, PITTSBURGH, PA.,
AND
J. Arnold Bargen, M.D.,
ASSOCIATE PROFESSOR OF MEDICINE, THE MAYO FOUNDATION, DIVISION OF MEDICINE, THE MAYO CLINIC, ROCHESTER, MINN.

(From St. Mary's Hospital on the Intestinal Service, The Mayo Clinic.)

Recent hematologic progress has been able sometimes to establish relations between a given hematologic picture and the clinical course of the disease. This work was undertaken to determine what value, if any, the analysis of the hematologic picture of patients who were suffering from chronic ulcerative colitis might have on the prognosis and treatment.

Dameshek,[7] Davidson and others,[8] Sours,[28] Watkins and Heck,[32] Watkins[31] and others, have written about the etiology, diagnosis and treatment of secondary and hypochromic anemias. The work of Arneth,[1] Cooke and Ponder,[5] Schilling,[27] Mullin and Large,[23] Farley, St. Clair and Reisinger,[11] Gorsky,[13] Eisenberg and Nemens[10] reveals that such information of prognostic value can be obtained from a study of the leukocytes. It was thought that a correlation of these separate studies might enhance our understanding of the hematologic picture of chronic ulcerative colitis. The pathology, bacteriology, local symptoms, and treatment are now well understood by many, but a description and application of information obtained from the hematologic picture have not been reported. This study was undertaken with the well-formulated general principles, which have been outlined by the previously named investigators, as a background. The material for this study consisted of the records of 100 unselected patients who were afflicted with chronic ulcerative colitis; this was augmented by a detailed study of 25 patients who were ill enough to be placed in the hospital.

One of us (Bargen)[2] has observed for years that patients who have chronic ulcerative colitis and who have not been treated have a markedly lowered value for the hemoglobin. A review of the records of the 125 patients substantiated this observation. There is moderate anemia, and in cases in which the condition is uncomplicated, the number of leukocytes is normal. The values for hemoglobin in this series, which were obtained with the photo-electrometer, ranged from 1.8 gm. to 16.7 gm. per 100 cc. of whole blood (average 11.1 gm.). The number of erythrocytes varied from 1,900,000 to 5,270,000 per cu.mm. In cases in which there was no complication, the number of leukocytes varied from 5000 to 10,000 per

* Former Fellow, The Mayo Foundation, Rochester, Minn.

cu.mm. of blood at the initial examination. The average color index was 0.77. The number of reticulocytes was within normal limits.

These figures were analyzed in many different ways. A study was made of the duration of the disease, the blood count, and hemoglobin when the patients first came under our observation. As a general rule, it can be said that there is no marked relationship between the number of erythrocytes, the value for the hemoglobin and the duration of the disease. The patients who had been ill for only a few months, as a rule, revealed a larger number of erythrocytes than did those who had been ill for longer periods. The patients who had been ill for more than 5 years also tended to have fewer erythrocytes per cu.mm. of blood and a lower value for the hemoglobin than did those who had been ill for a shorter time, but in a large majority of the cases there was little relation between these factors.

These cases also were analyzed to determine the relation between the number of erythrocytes, the value for the hemoglobin and the anatomic extent of the disease. Except for the 1 case of regional chronic ulcerative colitis in which the lesion was confined to the right half of the colon, there was no significant relation of these findings. There was a remarkable constancy between the value for the hemoglobin and the number of erythrocytes; the color index remaining close to 0.77.

It has been demonstrated that the secondary or hypochromic anemias may develop from many different causes,[16] such as acute or chronic hemorrhage, dietary deficiency,[17, 33] gastro-intestinal disturbances,[15] and chronic sepsis;[18, 22] finally, there is the idiopathic hypochromic type which is associated with or without achlorhydria.

Chronic ulcerative colitis is unique in that any of the previous factors might play a rôle in the production of the anemia. The chronic hemorrhage is undoubtedly the largest factor in producing anemia. The multitudinous bloody stools each day would be sufficient to produce grave anemia. In addition, there are the limitations in diet that frequently have been imposed on these patients. It is difficult to provide a diet which has a low residue and contains a large amount of iron;[3] at best, these diets are comparatively poor in this respect. The altered gastro-intestinal physiology,[16, 19] particularly the rapid transmission of food through the colon, would lessen the proper utilization and metabolism of foods which contain iron. A striking factor which probably contributes to the cause of the anemia, is the chronic sepsis. Many of these patients have a fever for months, which in itself would be sufficient to produce a moderately severe anemia by the action of the toxin of the specific diplostreptococcus.

Other data usually considered significant in the study of an anemia are unimportant here. The values for gastric acidity are usually within normal limits, the number of reticulocytes is only slightly

increased, the bleeding time and coagulation time are normal, and there apparently is no involvement of the central nervous system.

In cases of uncomplicated chronic ulcerative colitis the number of leukocytes ranges from 5000 to 10,000 per cu.mm. Of the 100 unselected cases there were 23 in which the number of leukocytes was more than 10,000 per cu.mm. At the time of the original examination, the largest number of leukocytes was 17,200. The average number of leukocytes in a case in which there were no complications was 8750 at the time the patient was admitted to the hospital. In every instance in which there was a persistence of more than 10,000, there was a complication of varying severity. There were instances of local complications such as perforation of the intestine or an ischiorectal abscess; or a more remote complication, as acute appendicitis, an infection of the upper part of the respiratory tract, or a flare-up of a quiescent distant focus, such as an abscessed tooth, acute tonsillitis, prostatitis, or iritis. In each case, as soon as the complicating factor was arrested, the number of leukocytes promptly returned to normal.

In some cases in which the patients were under close observation in the hospital, the number of leukocytes decreased to less than 2500 per cu.mm.; in 1 case it decreased to 2300, in another to 2000, and in a third to 1600. Subsequently, the number of leukocytes increased to normal in these cases. This leukopenia occurred in particularly virulent phases of the disease. A sharp decrease in the number of erythrocytes was associated with the leukopenia. As the general and local condition improved, both the number of the erythrocytes and leukocytes increased appreciably.

In general, the differential count was as follows: lymphocytes from 10 to 30%, neutrophils from 60 to 85%, monocytes from 2 to 30%, and eosinophils and basophils from 1 to 2% of the total number of leukocytes. Occasionally, a monocytosis was seen, in which the monocytes comprised 30% of the total number of leukocytes. The previous history and convalescence of these patients were no different from those of patients who disclosed normal leukocyte counts. In those cases in which complications occurred, the percentage of the various leukocytes rose to the expected levels. Neutrophils made up 85 to 95% of the total differential count; lymphocytes 5 to 10%; and monocytes, eosinophils, and basophils 1 to 2%. After the complications subsided, the various cells assumed their previous levels. When a monocytosis of 30% occurred, there was no immaturity or toxicity noted beyond the usual stages which normally are encountered in this disease. There is very little of prognostic or therapeutic value in a study of the differential count without special study of the cells.

Many features of the fundamental nature of chronic ulcerative colitis may be brought out in a detailed study of blood smears. The erythrocytes disclose marked hypochromasia as would be indi-

cated by the low color index. This is uniform and practically all of the erythrocytes share equally in the paucity of the hemoglobin. There also is considerable anisocytosis. A majority of the erythrocytes are slightly smaller than normal erythrocytes.

The leukocytes are of particular interest, and the features can be studied most easily in the neutrophils. These cells reveal many wide variations, but usually conform to a general pattern. The granules are considerably larger than the usual granules, and stain more deeply. A large number of vacuoles may be present. There is a very high percentage of non-filamented cells. Many of the same features can be seen in the monocytes, but they are not so clear cut as they are in the neutrophils and the findings are less obvious. All of these features in the neutrophils indicates a marked shift to the left and a very toxic process.

This investigation of chronic ulcerative colitis has been directed along two other lines. We have been materially aided in this study by the work of Mullin and Large,[23] and by the work of Farley, St. Clair and Reisinger,[11] on the filament-non-filament count and on the sedimentation rate. These two tests were studied in the hope that they might indicate whether or not these patients were "cured."

In cases in which chronic ulcerative colitis had not been treated, the filament-non-filament count was greatly altered. We have considered 16 non-filamented cells in each 100 leukocytes as the upper limit of normal. There were as many as 70 non-filamented cells among 100 leukocytes; the average was 17 filamented cells and 44 non-filamented cells at the time the patients were admitted to the hospital. As others have reported, the non-filament count increases and the filament count decreases with unfavorable progress. In 1 of the cases in which there was leukopenia, 78 of 80 neutrophils were non-filamented at the height of the exacerbation; no filamented cells were found for 3 consecutive days. In this disease, considerable favorable or unfavorable progress must be made before any alteration in the filament-non-filament count is noted. When a patient improves, the filament-non-filament count improves gradually, but progressively, until such time as proctoscopic and roentgenologic examination reveals that the patient is "cured" clinically when a normal filament-non-filament count obtains.

The sedimentation rate offers a fairly close corollary to the filament-non-filament count. These two laboratory procedures approximate each other closely in usefulness. We also found that the sedimentation rate was uniform in cases of chronic ulcerative colitis in which the patients had not been treated. There was very little relationship between the sedimentation rate and the extent of involvement or between the sedimentation rate and the duration and the anatomic situation of the disease. Increased sedimentation rates in these cases must be explained in terms of toxemia.[20] A sedimentation rate greater than 20 mm. has been considered ab-

normal. Very marked increases in the rate of sedimentation were noted in most of these cases. As in the case of the filament-non-filament count, marked and prolonged symptomatic improvement must take place before the sedimentation rate is appreciably altered. Those patients whom we considered as "cured," by all known criteria had a normal sedimentation rate. In exacerbations, the rate fell to approximately its original level, although the patients did not appear to be as ill as they were when they originally were observed. In contradistinction to the filament-non-filament count, the sedimentation rate shows the effect of extraneous factors more readily. Infections of the upper part of the respiratory tract, acute otitis media, and intestinal perforation, all alter the sedimentation rate greatly. The sedimentation rate promptly returns to its former level as soon as these incidental infections are successfully combated. Our experience would indicate that the sedimentation rate has less value than has the filament-non-filament count.

Comment. Study of the hematologic picture has brought out certain pertinent facts. It is probable that the decrease in the values for the hemoglobin and the decrease in the number of erythrocytes cannot be entirely accounted for on the bases of loss of blood, altered gastro-intestinal physiology, or inadequate diet. This is suggested further by the fact that in cases in which the degree of anemia is equal, the extent of involvement and severity of the disease may be entirely different; in one case the patient may lose much blood by the rectum, and in another case a minimal amount. Recent work by Robscheit-Robbins and Whipple[25] has suggested that production of hemoglobin is held in abeyance by severe infection. In cases in which the patients have not been treated, the value for the hemoglobin and the number of erythrocytes are in close relation to the severity of the infection. The reticulocytes are greatly increased; their number remains fairly constant. The metabolism of hemoglobin is probably much slower[26] than it is normally; hence the value for the hemoglobin is less than is commensurate with the nearly normal erythrocyte count.

Further evidence that chronic ulcerative colitis is a highly infectious disease is furnished by the observation of a marked shift of the leukocytes to the left, toxic changes in the leukocytes[23] and the greatly increased sedimentation rate.

Schilling,[27] Sours,[28] Mullin and Large,[23] and Gorsky[13] believed that, of all the hematologic evidence which indicates that a highly infectious process is in progress, a marked shift of leukocytes to the left is the most reliable and convincing. In chronic ulcerative colitis, this shift to the left is moderate or marked. The non-filamented leukocytes are very numerous and they show such evidence of severe toxic changes as large deeply staining granules, bizarre forms of nuclei and the inclusion of vacuoles.

Harvey and Hamilton[14] maintained that the hematologic picture is a mirror image of the focal process. In a case of uncomplicated

chronic ulcerative colitis in which the patient has not been treated, the number of leukocytes usually is normal. Sours[28] has shown that infection stimulates delivery of leukocytes from the bone marrow, and that the more severe the infection, the greater the number of cells which are given out by the marrow. In acute otitis media, Mullin and Large[23] explained the situation by saying that "when increased destruction occurs in infections, an increased demand is placed on the bone marrow and when it is unable to cope with the demand for mature cells, immature forms are poured out." Rarely is there a cell which is more immature than the metamyelocyte. The response to the stimulus is sufficient that further immature cells are not placed in the peripheral circulation. Judging by the high percentage of non-filamented forms, the infection must be very severe, but one must remember that a large region of the body is involved by the disease. A comparison of the following conditions will illustrate the profound toxemia of this infection. In chronic infectious arthritis, according to Steinbrocker and Hartung,[29] and Count, 31.5% of the leukocytes are non-filamented cells. In acute gynecologic diseases, 30 to 40% of the leukocytes are non-filamented,[21] in acute appendicitis, 30 to 50%.

When the demand for leukocytes suddenly becomes acute, as the result of increased toxicity, a leukopenia may develop. This is shown in the cases in which there were less than 2500 leukocytes in each cu.mm. of blood. Synchronous with the sharp decrease in the total number of leukocytes, the number of filamented cells may decrease to zero. Along with the sharp decrease in the number of leukocytes was a corresponding decrease in the number of erythrocytes and values for the hemoglobin. As the general condition improved, the number of filamented and non-filamented cells returned to the average for this disease. Schilling,[27] Sours,[28] Gorsky,[13] and Markowitz[21] interpreted the events as a temporary paralysis of the bone marrow with greatly increased peripheral destruction of cells. These cases correspond to Group 4 of Schilling's[27] classification, in which there is irritation of the bone marrow by the toxic process, and a resulting leukocytic response.

Another link in the evidence that chronic ulcerative colitis is a highly infectious disease, is the result obtained from a study of the sedimentation rate of the erythrocytes.[6, 20, 24, 32] Other conditions also may produce or increase in the sedimentation rate. Considering the rate of sedimentation which was obtained in cases of chronic ulcerative colitis in which the patients had not been treated, the test indicates a much more virulent and widespread infection than is present in the other diseases which have been mentioned. We believe this, along with the associated change in the leukocytes and erythrocytes, is significant.

In those cases of chronic ulcerative colitis in which clinical, proctoscopic, and roentgenologic examination indicated that the patients were cured, the number of leukocytes, the filament-non-

filament counts, and the sedimentation rates were normal. A normal sedimentation rate and a normal filament-non-filament count are not encountered in cases in which there is any sign of activity of the disease, as blood in the stools, tenderness over the colon, proctoscopic evidence of ulceration, or roentgenologic evidence of "feathery edges" of the colon. Many times, the problem arises as to the advisability of allowing a patient to relax his vigilance in the treatment of this prolonged disease, and it is of great importance to be able to substantiate an opinion of the absence of infection by the evidence offered by the sedimentation rate and the filament-non-filament count. The same criteria are used in the treatment and prognosis of such diseases as tuberculosis, acute rheumatic fever,[19] chronic infectious arthritis,[4] and pelvic infections.[21] In chronic ulcerative colitis, an additional aid is offered in making the differential diagnosis of symptoms which are the result of activity of the disease and those which are the result of narrowing of the rectum from scar tissue. In the latter instance, if other factors which affect the tests are controlled, the results of the filament-non-filament count will be well within the normal range. The results of these two simple procedures frequently govern the institution of surgical intervention, the omission of active treatment, and the relaxation of the constant vigilance.

This study also includes the rôle of the hemoglobin and the erythrocytes in the ultimate outcome of the disease. There is no gross relationship between the value for the hemoglobin, the number of erythrocytes, and the duration, extent, or anatomic situation of the disease. If, however, one separates the cases in which the value for the hemoglobin or erythrocytes is normal and those in which these values are subnormal, there will be a marked disparity in the duration of the disease. The average duration in the cases in which the value for the hemoglobin was normal was 1.3 years, as compared with 3 years in those cases in which the value for the hemoglobin was decreased.

It is a common procedure to base prognosis on the value for the hemoglobin and the number of erythrocytes.[9] In attempting to establish the relationship between the value for the hemoglobin and the duration of treatment, our attention was directed to ways and means of increasing the amount of hemoglobin and the number of erythrocytes. The standard treatment of hypochromic anemia is the administration of proper doses of some preparations which contains iron.[7, 8, 9, 12, 15, 17, 30, 31, 32] On account of the hyperirritability of the colon in cases of chronic ulcerative colitis, it is not always possible to administer therapeutic doses of iron without increasing the diarrhea. Reduced iron, ferric citrate, iron and ammonium citrate, pills of ferrous carbonate (Blaud's pills), ferric chloride and other similar preparations are administered with only fair success. In the cases in which it was possible to administer one of the drugs

in sufficient amount, definite and prompt improvement was noted in the general condition and in the local symptoms. Another method of increasing hemoglobin and erythrocytes is to resort to blood transfusions. Prior to this study, transfusions of blood often had been administered in cases in which there was a decrease in the amount of hemoglobin and in the number of erythrocytes. It would seem to be a good practice to administer transfusions of blood periodically until both the amount of hemoglobin and the number of erythrocytes are approximately normal in cases in which patients do not tolerate iron when it is administered orally. It is a well-established practice to administer repeated transfusions of 200 to 250 cc. of blood, rather than the usual 500 cc. If the latter amount is administered, the loss of blood through the rectum is greatly increased and only a small part of the original transfusion is utilized. Transfusions of 200 to 250 cc. usually are well utilized and do not cause any disturbance. Occasionally, amounts as small as 100 cc. are indicated. After the amount of hemoglobin and the number of erythrocytes have returned to normal, it frequently is possible to administer one of the preparations of iron in sufficient amounts in order to maintain the normal amount of hemoglobin and the normal number of erythrocytes. Those patients who receive transfusions until these constituents of the blood are normal, experience a sharp gain in general well-being and a secondary improvement in the intestinal disturbance. These aids are not of primary importance but are valuable additions to the treatment which has been outlined by one of us (Bargen).[2]

As a control, we studied a group of cases of amebic dysentery and a group of cases in which the diagnosis was irritable colon and so-called "colitis." In cases of amebic dysentery, the value for the hemoglobin and the number of erythrocytes was normal. The number of leukocytes was essentially the same as it was in the cases of chronic ulcerative colitis. In cases of uncomplicated amebic dysentery the number of leukocytes was normal, but the non-filamented cells were increased, the average being 47% of the total leukocytes. The sedimentation rate also was increased.

In cases of irritable colon, the value for the hemoglobin and the number of erythrocytes were entirely within normal limits. Enumeration of the leukocytes and differential counts did not reveal any abnormality. The sedimentation rate and the filament-non-filament counts were normal.

While we were engaged in this study, a patient who had primary hypochromic anemia[8] with normal gastric acidity and marked diarrhea was under our observation. The number of leukocytes ranged from 3500 to 4000 per cu.mm. of blood, but a normal filament-non-filament count obtained, and the sedimentation rate also was within the normal range.

Summary. Chronic ulcerative colitis reveals the picture usually seen in severe infectious processes.

Transfusions of 200 to 250 cc. of blood appear to be the most efficacious means of increasing the amount of hemoglobin and the number of erythrocytes. A marked subjective and objective improvement was noted when these constituents of the blood approached normal.

Administration of some preparation of iron, in therapeutic dosage, is necessary to maintain the normal amount of hemoglobin and the normal number of erythrocytes.

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FURTHER OBSERVATIONS ON PARENTERAL LIVER EXTRACT THERAPY IN PNEUMONIA.

By J. Alfred Wilson, M.D.,
attending physician, meriden hospital, meriden, conn.,
and
William C. Carey, M.D.,
meriden, connecticut.

With the Technical Assistance of Florence Hafner.

The use of parenteral liver extract in 2 cases of streptococcus pneumonia has been previously reported by one of us.[9] In this

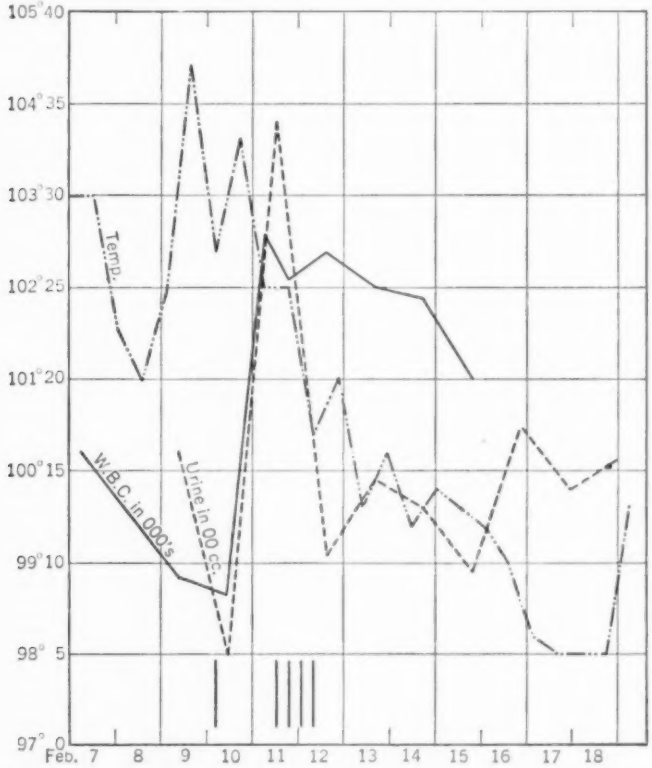
paper, the results obtained in 28 additional cases treated with parenteral liver extract are reported, making a total of 30. These include 8 streptococcus pneumonias, 1 staphylococcus, and in the remainder the pneumonococcus was most frequently found to be the causative organism. Five of the 30 cases died, a mortality of 16.7%. Five cases were treated in their homes; the other 25 were private and ward patients in the Meriden Hospital. Two children are in the series. All were cases of pneumonia with a leukopenia or falling leukocyte count; 3 were pneumonias occurring in the course of a streptococcus septicemia and 2 of these septicemias were the only cases to receive serum. They were given intravenously polyvalent antistreptococcic serum. No antipneumococcic serum was used.

A leukocyte count of over 15,000 was present in only 8 cases at the beginning of treatment; the rest were under 15,000. Cases of pneumonia with a high sustained leukocyte count were not treated with parenteral liver and are not included in this discussion. In the group which was given liver extract therapy the prognosis was not good from the point of view of clinical status and leukocytosis. This was demonstrated by Middleton and Gibbon[4] who studied 164 cases of pneumonia in a hospital practice and found that a leukocyte count above 20,000 indicated a much better prognosis than a count below this level. Fleming[2] studied at the Glasgow Infirmary the leukocytosis in typed lobar pneumonia, serum treated. "Of the total 147 cases (with 21 deaths) 30 failed to exceed 10,000 cells, and this number contained 33% of the total deaths. The 47 cases which had counts of 15,000 and under included 62% of the total deaths. For this reason it has been found useful to regard a count of 15,000 or more as an 'adequate' leukocytosis during the acute illness." His findings also indicated the age of the individual governed the prognosis. A leukopenia in a patient over 40 years of age indicates an unfavorable prognosis.

Insufficiency of the bone marrow has been discussed recently by Middleton and Meyer.[5] They believe a leukopenia may reflect a partial leukogenetic failure of the bone marrow and that bone marrow may be stimulated by treatment, probably by chemotaxis. Following their line of thought, it seems possible that pneumonia may more often occur in individuals whose leukogenetic function is below normal than in persons whose leukogenetic functions are normal. If this is the case, it seems rational to use some therapy that would stimulate the bone marrow activity.

When Murphy[7] showed that liver extract stimulated the bone marrow of pernicious anemia to greater erythropoietic activity, he also called attention to the fact that leukopoiesis was stimulated. Powers, Murphy, and Humphreys,[8] in a study of the effect on normal individuals of parenteral liver extract, found a definite increase in the white blood cell count in 21 normal subjects. There was a 94%

increase in ambulatory persons and a 72% increase in recumbent persons. The peak of the leukocyte count was reached in about 7 hours after the injection, then the count slowly returned to normal. Meyer, Middleton, and Thewlis[3] using parenteral liver found an increase of leukocytes in 4 cases.

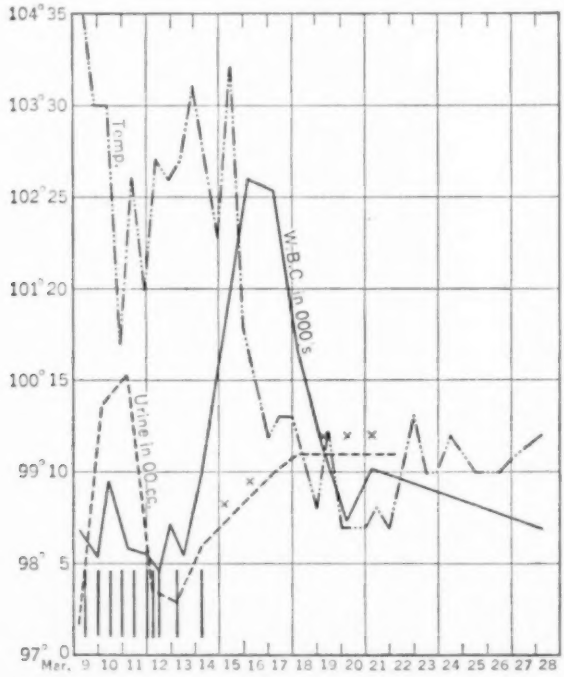


GRAPH 1.—LEUKOCYTE COUNT, TEMPERATURE, AND URINE OF CASE 1. The straight line is the leukocyte count in thousands; the dotted line the temperature taken in the morning and in the evening; the broken line the urine in hundred cc.; the vertical lines are injections equivalent to 150 gm. of fresh liver.

Thus, the rationale of the use of parenteral liver extract therapy may be summarized as follows: 1, Parenteral liver extract stimulates leukocytosis; 2, in some pneumonias the blood picture is characterized by a relative leukopenia or a falling white blood count; 3, these cases offer a more unfavorable prognosis; 4, therefore, parenteral liver extract given to these cases should stimulate leukocytosis and as a secondary effect improve the clinical picture and progress.

Method of Treatment. The concentrated liver extract was injected intramuscularly in varying amounts, depending on the severity of the infection and the leukopenia developing during the course of the disease. The

injections were made deep into the muscles in the buttock and deltoid regions. The average amount was 6 cc. a day. In 1 case 16 cc., the equivalent of 800 gm. of fresh liver, was given during 24 hours with a very satisfactory result. Lately we have given by injection 2 to 4 cc. of liver extract using extract equivalent to 100 gm. of fresh liver every 6 to 8 hours. It has been shown[8] that the count reaches its peak in 7 hours after the injection. A majority of the patients were kept in oxygen tents as long as dyspnea and cyanosis were present. Expectorants, such as ammonium chloride, were given in gr. 10 doses every 2 to 4 hours. Morphine and codeine were given for severe pleural pains. In case of beginning heart failure during the time of the crisis, digalen 20 drops and strychnine gr. 1/40 with or without atropine sulphate gr. 1/100 were given hypodermically at 4-hour intervals 3 or 4 times. No digitalis was given at any other time and no cases were digitalized. An effort was made to keep the fluid intake between 3000 and 4000 cc. daily. Liquid and soft diet were given in small amounts frequently. Whiskey was prescribed in small amounts for elderly persons. Quiet and rest were particularly sought, and several of the patients had the benefit of private nursing care. No purgatives were allowed. If constipation became marked, normal saline enemas were given.



GRAPH 2.—LEUKOCYTE COUNT, TEMPERATURE, AND URINE OF CASE 24.
The straight line is the leukocyte count in thousands; the dotted line the temperature taken in the morning and in the evening; the broken line the urine in hundred cc.; the days marked x it was involuntary; the vertical lines are injections equivalent to 200 gm. of fresh liver.

Results of Treatment. There was an approximate increase in leukocyte count of 70% and the range was from 6 to 239% increase.

This is based on counts taken in some cases twice a day and can only be approximate because it has been shown[8] that the count will vary from hour to hour, and after an injection of concentrated liver extract the leukocyte count gradually rises for 7 hours, then gradually falls. All but 6 cases responded by an increase in leukocyte count. There was a daily drop in the white blood count until liver extract treatment was started. This is usually considered a very ominous sign. One of the cases which had a count above 15,000 was a case of Type III pneumococcus in which the count was 22,400 at the beginning of liver injections. The count rose to 30,400 and the patient made a complete recovery. Several patients showed a marked increase in urinary output the day after parenteral liver was given, confirming the observation made in the first case studied[9] and apparently establishing the fact that parenteral liver extract stimulates the kidneys to greater urinary output. No anaphylactic reactions occurred either locally or generally. Graph 1 gives the reaction that resulted a few hours after liver extract was given. Graph 2 gives the rise that occurred in leukocytes after 6 days of liver injections. This appeared to be a delayed reaction. The count averaged 5000 for 6 days, then in 3 days rose to 25,000. Recovery then took place.

Fatal Cases. The first instance in which death occurred was a woman, aged 38, who died on the tenth hospital day and who had been ill 4 days before entering the hospital. An autopsy showed many fine abscess cavities throughout both lungs from which staphylococci were cultured. This was regarded as a staphylococcus pneumonia although it may have been a mixed infection like those reported by Finland,[1] who found that 133 out of 2000 indicated a primary pneumococcus with a staphylococcus or streptococcus infection superimposed. The second case to die was a chronic alcoholic who had been ill 2 weeks, beginning with a marked diarrhea and fever followed by jaundice. He died from an apparently terminal pneumonia. The liver extract was started the day before death with no improvement and a very slight rise in leukocytes, then a moderate fall before death. The third case to succumb was a man of 32 who had a Type III pneumococcus infection. His white blood count fell from 18,000 to 2000 in 3 days and he failed rapidly and died on the fifth day of his illness despite liver therapy. The fourth case to die was one of streptococcus septicemia following a very acute pharyngitis, cellulitis of the right arm, and lobar pneumonia at the base of the left lung. Liver extract was given daily for 5 days. The leukocyte count remained between 4000 and 9000. On the seventh day it rose to 17,600 and on the eighth to 26,000. The temperature then subsided. The abscess in the right arm was incised. The patient did very well and was out of bed a short time on the nineteenth and twentieth days. During the evening of the twentieth day the patient died suddenly of a pulmonary embolus.

TABLE 1.—CLINICAL DATA ON 30 CASES OF PNEUMONIA.

Case No.	Sex.	Date.	Age (yrs.).	Organism.	W. B. C. (thous.)			Urine (100 cc.).			Liver extract (gm.).	Remarks.	Recovered or expired.
		1934			(1)	(2)	(3)						
1*	M.	2/10	45	Strep.	8.2	27.8	26.8	16.0	5.0	34.0	800	L. U. Lobe. Marked toxemia. Delirious	Rec.
					(See Graph 1)								
2*	F.	5/22	38	Staph.	14.6	15.2	18.0	9.0	23.0	12.0	1250	L. U. Lobe. 2 neg. and 1 pos. blood cultures. Ill 12 days	Exp.
3*	F.	7/18	21	Strep.	5.2	7.2	12.2	3.0	6.0	10.0	1400	L. U. Lobe. Yellow sputum. Good recovery	Rec.
4	M.	9/8	40	Strep.	8.2	12.2	14.0	..	..	..	950	R.L. Lobe. Pleurisy but no effusion. Treated at home. Bright red sputum	Rec.
5*	F.	9/18	19	II	8.2	8.0	8.8	10.5	10.0	10.0	600	L. L. Lobe. Pleurisy but no effusion. Very ill after pneumothorax	Rec.
6*	F.	12/19	45	....	8.2	11.2	9.4	13.5	18.0	20.0	1100	L. L. Lobe. Long convalescence	Rec.
7*	M.	12/27	22	Strep.	5.8	6.4	9.0	22.0	22.5	27.5	800	L. L. Lobe. Not very toxic	Rec.
8*	F.	12/28	62	Strep.	8.4	15.2	21.8	3.0	14.5	25.0	600	R. L. Lobe. Not very toxic. Slow recovery	Rec.
9*	M.	12/30	35	III	19.2	19.8	2.0†	7.0	7.0	12.8	1700	Left lung. Pos. blood culture. Rapidly fatal	Exp.
10*	F.	12/30	32	Strep.	9.6	13.4	15.0	6.0	17.9	9.5	450	R. L. Lobe. Prolonged convalescence	Rec.
		1935											
11*	M.	1/2	14	....	12.6	8.0	12.4	8.5	15.5	10.5	1050	R. L. Lobe. Light attack. Good recovery	Rec.
12	M.	1/5	42	....	8.0	6.6	15.0	4.8	31.5	20.0	1000	L. L. Lobe. Pleurisy but no effusion. Treated at home. Very ill few days	Rec.
13	M.	1/6	56	....	8.0	9.0	7.8	..	..	..	600	Bronchopneumonia following coronary attack	Rec.
14*	F.	2/15	45	III	22.4	24.8	30.4	11.0	18.5	12.0	500	Bronchopneumonia. Not very toxic. Good recovery	Rec.
15*	M.	2/28	40	Neg. I, II, III	14.8	17.8	26.3	..	..	..	850	L. L. Lobe. Second attack pleurisy—no empyema. First had empyema	Rec.
16*	M.	3/22	45	....	13.6	13.0	10.6	..	..	..	900	R. U. Lobe. Chronic alcoholic. Liver given last 24 hours	Exp.
17*	F.	10/12	59	Strep.	13.8	15.8	24.2	15.7	17.0	11.0	900	R. L. Lobe. 1 neg. blood culture. Good recovery. 6 days	Rec.
18*	F.	10/26	72	....	4.6	9.0	12.6	6.5	10.5	6.5	900	R. L. Lobe. Treated at home several days	Rec.
19	F.	11/18	69	No sputum	3.4	3.2	7.6	..	..	..	4150	L. L. Lobe. Quite toxic. Pernicious anemia. R. B. C. 1,520,000	Rec.
		1936											
20*	F.	1/10	50	....	10.8	20.8	18.0	..	..	..	200	R. L. Lobe. Influenza type. Treated at home	Rec.
21	M.	2/20	54	....	16.6	16.5	20.0	..	..	..	250	R. L. Lobe. Treated at home. Good recovery	Rec.
22*	F.	2/24	75	Strep.	20.0	20.0	25.0	9.0	14.5	11.5	1550	R. L. Lobe. 1 pos. 12 hr. blood culture. Complication of infected foot and septicemia	Rec.
23*	F.	3/3	43	Strep.	17.8	17.4	19.0	8.0	10.0	13.0	1000	L. L. Lobe. 2 neg. blood cultures. Pleurisy but no effusion. Streptococcus septicemia. Died of embolus on 25th day	Exp.
24*	F.	3/9	75	III	6.8	5.6	26.0	Involuntary			2000	Both bases. 2 neg. blood cultures. Very excellent recovery. Diabetes mellitus, insulin given. Blood sugar 375 mg.	Rec.
					(See Graph 2)								
25	F.	3/14	68	....	14.0	10.6	14.0	..	..	..	700	L. L. Lobe. Coronary attack. Treated at home	Rec.
26*	M.	3/28	36	Strep.	11.8	23.4	19.8	12.0	15.7	13.5	2900	Infarct both lungs. Pos. blood culture. Streptococcus septicemia. Pneumonia complication of infection. Very ill. Good recovery	Rec.
27*	F.	3/31	75	IV	16.4	12.2	14.4	9.5	11.7	20.5	2800	Bilateral pneumonia. Neg. blood culture. Good recovery	Rec.
28	F.	4/26	38	XXI	3.8	4.6	5.2	3.6	3.6	4.0	2700	R. L. Lobe. Neg. blood culture. Terminal pneumonia. Malignant hypertension	Exp.
29	M.	5/4	45	....	30.0	25.2	24.4	..	..	..	1700	L. L. Lobe. Very ill at home 5 days before hospitalization. Severe epistaxis	Rec.
30	M.	5/5	57	V	23.0	20.6	13.0	..	..	..	1200	L. U. Lobe. Lobar 4 days' duration on entrance. Blood sugar 250 mg.	Rec.

* Indicates that the clinical diagnosis was confirmed by Roentgen ray.
† Last count before death.
(1) under W. B. C. is the count before liver injection;
(2) is the count 7 hours after the injection, or, where that was not available, the next day;
(3) is the highest count during the liver therapy.

The fifth fatality was a single woman, aged 42. She had been suffering from a malignant hypertension for 5 years and her pneumonia was a terminal condition. She was ill 6 days. She failed very rapidly. Her blood cholesterol was below 100 mg. before death. This case was included in the series because she was given the parenteral liver extract.

Discussion. We are well aware that a group of 30 cases of pneumonia are all too few from which to draw any definite conclusion, and we do not wish to compare the parenteral liver treatment with the many other treatments of pneumonia. We simply wish to record our experiences. As we have used this treatment over the last 3 years, we have continued to be impressed with its possibilities.

Our mortality rate of 17% appears favorable. In this same hospital there was a mortality of 33.5% in all pneumonias during 1933.[6] The 5 cases that succumbed were very ill and after close study we doubt if any method of treatment would have been successful. Twenty-two of the group were 40 and over, ranging up to 75 years; 2 of this group died, giving a mortality rate of 9%. One of these was the case that suffered a sudden pulmonary embolus on the twenty-second day.

The parenteral liver treatment is safe, simple to give, very economical, free from serum sickness and anaphylactic reactions. The only objection is the pain that occurs at the site of the injection. This is moderate and of short duration.

After studying the blood counts in pneumonia one cannot help but be impressed by the poor reaction of the bone marrow in a considerable percentage of pneumonias and by the falling white cell counts that occur in many of the critically ill patients. Does "insufficiency of the bone marrow" as put forth by Middleton[5] predispose these individuals to pneumonia?

Conclusions. 1. Thirty cases of pneumonia treated with parenteral liver resulted in recovery in 83%.

2. The use of parenteral liver extract was accompanied by a significant rise in the white blood count in all but 2 cases and clinical improvement occurred simultaneously.

3. In the great majority of the cases there was an increased urinary output following the injection of parenteral liver.

4. The treatment is safe, economical, and free from serum sickness. It causes moderate pain at the site of injection.

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THE USE OF P-AMINOBENZENESULPHONAMIDE IN TYPE 3 PNEUMOCOCCUS PNEUMONIA.

J. H. L. Heintzelman, M.D.,
ASSISTANT, DIVISION OF MEDICINE, THE WESTERN PENNSYLVANIA HOSPITAL,
By Philip B. Hadley, Ph.D.,
CHIEF, BACTERIOLOGICAL SERVICE, THE WESTERN PENNSYLVANIA HOSPITAL,
AND
Ralph R. Mellon, M.D.,
DIRECTOR, INSTITUTE OF PATHOLOGY, THE WESTERN PENNSYLVANIA HOSPITAL,
PITTSBURGH, PA.

(From The Institute of Pathology and the Medical Division (Frank A. Evans, M.D., Chief) of The Western Pennsylvania Hospital.)

Although Domagk[2] reported that the therapeutic effect of Prontosil* in animals was strictly specific for streptococcus and staphylococcus, but ineffective against pneumococci, Hörlein[4] has obtained contradictory results with the latter, some being negative, and others positive. Inasmuch as no experimental data were given, a well considered opinion is impossible. No mention is made of tests with the para-amino compound.

The favorable outcome of the experiments of Rosenthal[5] on the influence of p-aminobenzenesulphonamide on Type 1, 2 and 3 pneumococcic infections in mice, and of the studies of Cooper, Gross and Mellon[1] and of Gross and Cooper[3] on Type 3 infections in white mice and white rats, appeared to justify a study of the influence of this therapeutic agent on patients suffering from lobar pneumonia due to the Type 3 pneumococcus.

Opportunity for such a study was presented by the unusually high incidence of Type 3 pneumonia infections occurring in the Pittsburgh area during the present pneumonia season.†

According to our records, Type 3 cases began to appear early in the season (September) and came to a peak with 11 cases in January. After this period, which also marked the height of the influenzal infections, the number diminished during February (2 cases) and

* Three sulphonamide compounds have been used in this form of chemotherapy: (1) Prontosil I, which is the hydrochloride of 4′-sulphamido-2, 4-diaminoazobenzol; (2) Prontosil II (or S) is the di-sodium salt of 4′-sulphonamide-phenol-azo-1-oxy-7-acetylamino-naphthalin-3, 6-disulphurous acid; (3) para-amino-benzenesulphonamide. These compounds have been introduced commercially under various trade names.

† That the higher incidence of Type 3 pneumonia during the present season has not been peculiar to Pittsburgh alone is demonstrated by information received from hospitals in New York City, Albany, Buffalo, Cleveland and Philadelphia. On the other hand, it should be noted that, in some of the cases here reported, we may not have been dealing with wholly typical Type 3 lobar pneumonia, but a type of infection perhaps comparable with some of the influenzal pneumonias that occurred during the 1917–1918 influenza epidemic. This probability is enhanced by the fact that the majority of the Type 3 cases here reported occurred during the recent influenza-like epidemic in Pittsburgh; and that the number of Type 3 cases diminished rapidly as the wave of influenzal infection subsided. Moreover, Type 3 pneumococci were observed in the sputums of a few patients in which characteristic pneumonia did not develop, although no Type 3 organisms were found in cultures from the throats of 15 influenza patients.

March (2 cases). This rather remarkable increase in Type 3 cases was not only actual, but relative; for, from the beginning of the pneumonia season and continuing through January, the number of Type 3 cases under observation exceeded the number of Type 1 and 2 cases combined. At the time of writing (March), the number of Type 1 and 2 cases is again rapidly mounting, and this new trend is accompanied by a corresponding decrease (both actual and relative) in the number of Type 3 infections.

In this paper there are reported 19 cases of Type 3 pneumonia. Of these, 9 were treated with p-aminobenzenesulphonamide (Prontylin) and 10 received no special form of treatment. These cases occurred from September to March, inclusive; and the majority were under observation during January. By late February and in March, Type 3 cases were comparatively rare.

The typings were done by the Neufeld method from sputum, and from positive blood cultures when available. In view of the cross-reactions that often occur between Types 3 and 8, a special effort was made to rule out Type 8 infections in the present series. In only 1 case (M. G., treated) was a difficulty experienced in distinguishing between these 2 serologic types. One piece of evidence supporting the authenticity of the type-diagnoses lies in the circumstance that, during the period of study, there occurred in this hospital 6 cases of Type 8 pneumonia, all except 1 of which recovered. Their differentiation from Type 3 presented no special difficulty. Type 4, 5, 6 and 7 cases manifested about normal incidence during this period.

Treatment consisted of the oral administration of p-aminobenzenesulphonamide (Prontylin) which, in a few cases, was augmented by intramuscular injections of Prontosil. Owing to the late arrival in the hospital of some of the patients, the first administration of sulphonamide was sometimes considerably delayed.

With reference to predisposing factors, complications, age, etc., there was a general similarity between the 2 groups (treated and untreated), although these factors were somewhat more favorable to the treated group. For example, in the untreated group there was 1 patient with an asthmatic condition, 1 with a slight myocarditis and 1 that was an alcoholic; these were among the patients that died. In the treated group, on the other hand, in 1 patient the Type 3 infection was superimposed upon a Type 7 pneumonia; and this patient recovered. Positive blood cultures were obtained from 2 patients of the untreated group and from 1 patient in the treated group; all 3 patients died.

While a bacteremia is now generally recognized as of serious prognostic import, what many regard as the *critical* or recovery level (30 colonies per cc.) may vary from season to season within wide limits. In this connection the results of Dr. George H. Robinson, Bacteriologist of the Allegheny General Hospital, seem pertinent.

Six of Dr. Robinson's 7 fatal Type 3 bacteremic cases were well

within the critical level—4 of these being essentially negative (one colony or less per 10 cc. of blood). Yet they all died in this influenza season[8] While the private nature of many of our cases made it impracticable to do serial blood cultures, the conditioned nature of this criterion would in any event make necessary the treatment of larger numbers of cases in order to assess properly the value of the drug.

As to age incidence, the situation slightly favored the treated group. The average age of the treated patients was 44.4 years; that of the untreated, 49.2 years. In the treated group the only 2 patients that died were the 2 oldest (60, 67). In the untreated group the only patients that recovered were (with one exception) the 2 youngest (31, 39), the exception being an alcoholic (36). In both groups, age was clearly a modifying factor; but the influence of increased age as a factor militating against survival appeared to be less marked in the treated than in the untreated group.

TABLE 1.—UNTREATED HOSPITAL CASES.

Case No.	Initials.	Sex.	Age, yrs.	Onset.	Entered hosp.	Remarks.	Died.
1	T. C.	M	49	1/10/37	1/14/37	Lobar pneumonia, Type 3; left base; following influenza; blood culture for pneumococcus Type 3 positive	1/14/37
2	R. N.	M	64	11/30/36	12/ 8/36	Bilateral lobar pneumonia, Type 3; no complicating features; blood culture negative	12/ 8/36
3	M. E.	F	60	11/16/36	11/23/36	Bilateral lobar pneumonia, Type 3; asthmatic condition present; no blood culture taken	11/25/36
4	A. E.	F	53	10/ 4/36	10/ 5/36	Bilateral lobar pneumonia, Type 3; blood culture negative; no complicating conditions	10/ 7/36
5	J. M.	M	42	9/12/36	9/15/36	Bronchopneumonia, Type 3; myocarditis present; no blood culture taken	9/16/36
6*	D. P.	M	39	11/26/36	12/ 1/36†	Bronchial pneumonia, Type 3; no complications; no blood culture taken	Recovered.
7*	W. S.	M	31	Prev. to 11/29/36	11/29/36†	Lobar pneumonia, Type 3; right middle lobe; no complications; no blood culture taken	Recovered.
8*	M. S.	F	54	1/ 7/37	Treated at home.	Double lobar pneumonia, Type 3; no complications; no blood culture taken	6th day of disease.
9	J. McK.	M	36	Prev. to 1/15/37	1/16/37	Bilateral lobar pneumonia, Type 3; alcoholism; blood culture negative (Prontylin begun 1/16/37; discontinued after 25 gr.).	1/18/37
10	D. McC.	F	64	?	3/12/37	Lobar pneumonia, left base; blood culture positive 3/12/37; no complications	3/13/37

* Outside cases. † Seen by physician.

While it is true that the average delay in entering the hospital after onset was slightly greater in the case of the untreated group (4.2 days) than in the treated group (2.6 days), it is not believed that this was a factor of great significance. Indeed, the 2 cases that recovered in the untreated groups were not hospital cases. Delay in entering the hospital may have had an influence in 2 or 3 cases (untreated group) that did not enter until the eighth or ninth day of illness, and died soon afterward. These patients, however, also happened to be the oldest of the group.

Tables 1 and 2 present briefly the circumstances surrounding each observed case in both groups:

These observations, together with data compiled on 33 additional cases of alleged Type 3 pneumonia occurring in Pittsburgh during the same period, are summarized in Table 3:

Summary and Conclusions. It has been shown that in a group of 9 cases of Type 3 pneumonia treated with p-aminobenzenesulphonamide, 7 patients recovered and 2 died. In a corresponding group of 10 patients observed approximately during the same period, but not receiving sulphonamide treatment, 2 patients recovered and 8 died. In a group of 33 cases in the Pittsburgh area, but not

TABLE 2.—TREATED HOSPITAL CASES.

Case No.	Initials.	Sex.	Age, yrs.	Onset.	Entered hosp.	Remarks.	Died.
11	C. J.	M	30	1/ 6/37	1/ 9/27	Lobar pneumonia, Type 3; left side with pleural effusions; blood culture negative; Inf. started as Type 7 pneumonia; recovery after administration of Type 5–7 pneumococcus serum; Type 3 infection superimposed on 1/18/37; Prontylin from 1/19/37 (5 gr. each 2 hours) to 1/27/37; few intramuscular injections of Prontosil given	Recovered.
12	J. McA.	M	67	1/15/37 or before	1/16/37	Lobar pneumonia, Type 3, right base; no complications; blood culture positive for Type 3 pneumococcus; Prontylin by mouth 1/21/37 (10 gr. each 2 to 4 hours); discontinued 1/27/37	1/31/37
13	T. S.	F	60	About 1/16/37	1/19/37	Bilateral lobar pneumonia, Type 3; blood culture negative 1/21/37; no complications; Prontylin by mouth 1/21/37 and 1/22/37 (5–10 gr. every 2 hours)	1/24/37
14	L. A.	F	54	1/17/37	1/24/37	Lobar pneumonia, Type 3; right upper lobe; blood culture not taken; no complications; Prontylin 1/24/37 (10 gr. every 3 hours); discontinued 1/26/37	Recovered.
15	C. S.	F	46	1/29/37	1/31/37	Unilateral lobar pneumonia, Type 3; no complications; no blood culture taken; Prontylin by mouth 2/1/37 (5 gr. every 2 hours); discontinued 2/10/37	Recovered.
16	M. G.	M	33	About 2/15/37	2/16/37	Lobar pneumonia, Type 3; no complications; blood culture negative 2/16/37; Prontylin soon after diagnosis (10 gr. every 2 to 3 hours) by mouth; also received few intramuscular injections of Prontosil; treatment discontinued 2/24/37	Recovered.
17*	M. McC.	F	32	1/27/37	1/27/37†	Lobar pneumonia, Type 3; right side and lower left lobe involved; no complications; no blood culture taken; Prontylin by mouth first day of illness and continued in gradually decreasing doses (40 to 15 gr. daily)	Recovered.
18*	M. P.	F	40	Prev. to 1/20/37	1/20/37†	Lobar pneumonia, Type 3; no blood culture; Prontylin (exact dates uncertain) (30 to 50 gr. per day) continued for 4 or 5 days; few intramuscular injections of Prontosil	Recovered.
19	S. B.	F	38	1/25/37	1/26/37	Lobar pneumonia, Type 3; right middle lobe, not severe involvement; blood culture negative; Prontylin by mouth 1/26/37 (5 gr. every 4 hours) continued for 5 days	Recovered.

* Outside cases. † Seen by physician.

TABLE 3.—RESULTS OF TREATMENT IN TYPE 3 PNEUMONIA.

	Cases treated.					Cases untreated.				
Group.	Cases.	No. died.	% died.	No. recov.	% recov.	Cases.	No. died.	% died.	No. recov.	% recov.
Reported series .	9	2	22	7	78	10	8	80	2	20
Other cases . . .	..	..	..	..	..	33	24	73	9	27
Totals	..	..	..	..	..	43	32	74	11	26

under our direct observation, 9 patients recovered and 24 died. The mortality rate for all untreated patients was 74%; that for the treated patients, 22%.

Despite the fact that the number of treated Type 3 cases here reported is small, and that the treated group was somewhat favored

by the factors of age incidence and by the absence of significant complicating features, the nature of the difference in relative mortality in the treated and untreated groups appears to justify continued application of the treatment of Type 3 pneumonias by p-aminobenzenesulphonamide until a sufficient number of cases have been accumulated to justify a final judgment as to the efficacy of this mode of therapy. Particularly is this to be emphasized in light of circumstances which made it impracticable to carry out serial blood culture studies.

SUPPLEMENTARY NOTE.—Since going to press 4 additional cases have been treated. Two of these received the treatment within 48 hours after the onset and made a prompt recovery. The other two died in about 12 hours after entering the hospital, thus precluding an effective administration of the drug.

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SPONTANEOUS HEMOPNEUMOTHORAX.

REPORT OF THREE CASES WITH A REVIEW OF THE LITERATURE.

BY HENRY U. HOPKINS, M.D.,
INSTRUCTOR IN MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

(From the Medical Clinic of the Hospital of the University of Pennsylvania.)

ALTHOUGH traumatic hemopneumothorax occurs fairly frequently as a complication of crushing or penetrating wounds of the chest and is discussed in standard treatises on thoracic surgery, spontaneous hemopneumothorax is much less common and one finds few references to it. However, it is probably more common than the recorded cases would indicate. Many doctors hesitate to report a single case, or do not realize the apparent infrequency of this condition. For example, when Wilson[37] read his paper reporting 2 cases, the discussion brought to light 7 others, previously unreported. It is possible that in some instances the hemorrhagic nature of the fluid is not recognized, and a diagnosis is made of spontaneous pneumothorax with effusion. In fact, spontaneous hemopneumothorax undoubtedly represents merely a spontaneous pneumothorax in which unusual conditions are present to give rise to a greater or lesser amount of bleeding into the pleural cavity. Unless thoracentesis becomes necessary for the relief of dyspnea, or unless signs of internal hemorrhage become conspicuous, an exploratory puncture may never be done. I wish to present briefly the records of 3 cases, discuss the etiology and treatment, and call attention to other recorded cases (Table 1).

TABLE 1.—ANALYSIS OF RECORDED CASES OF SPONTANEOUS HEMOPNEUMOTHORAX.

Author.	Age.	Side.	Treatment* amount removed.	Result—Remarks.
Pitt[29] (Case 2)	40	?	?	Fatal; tuberculous cavity.
Heise and Krause[13]	21	L	400 cc.	Fatal; receiving art. pneumothorax.
Sardo[31]	?	L	"Bloody fluid"	Recovery; was receiving bilat. pneumothorax for pulm. tubere.
Leggett, *et al.*[22] (Case 2)	?	?	"Repeated"	Recovery. Receiving art. pneumothorax.
Sergent[32]	31	L	1550 cc.	Recovery. Receiving art. pneumothorax for 3 years
Allan[2] (Case 1)	20	L	Thor.	Recovery. Probable tuberculosis later.
Allan[2] (Case 2)	38	R	Thor.	Recovery. Probable tuberculosis later.
Patino Mayer and Pataro[26]	32	R	?	Recovery. "Latent tuberculosis."
Holden[16] (Case 1)	32	L	1000 cc.	Recovery. Tuberculosis later (?).
Wilson[37] (Case 2)	30	L	800 cc.	Recovery. Tuberculosis proven. Subsequent thoracoplasty.
Korol[20] (Case 2)	38	L	?	Recovery. Tuberculosis later. Vesicle seen by Roentgen ray.
Pitt[29] (Case 1)	18	R	Thor.	Fatal: bulla and torn adhesion found.
Rolleston[30]	21	R	Thor.	Fatal: bleeding point not found.
Boland[4]	34	R	2170 cc.	Recovery.
Ness and Allan[25]	31	L	Thor.	Recovery.
Rushby[6]	17	L	500 cc.	Recovery.
Williamson[36]	?	L	10,000 cc.	Recovery.
Fischer[11]	22	R	Thor.	Fatal. Diagnostic error led to laparotomy.
Kiaer[18]	30	L	"Air and blood evacuated"	Fatal. No break found in pleura; no source of bleeding.
Bouchut and Beaupere[5]	21	R		Recovery.
Doria[10]	26	R	930 cc.	Recovery. Fluid replaced by nitrogen.
Hurxthal[15]	29	R	3400 cc.	Recovery. Fluid replaced by air.
Terry[34]	34	L	950 cc.	Recovery. Oxygen tent for dyspnea; transfusion for bleeding.
Palmer and Taft[27] (Case 1)	26	L	"Large amount"	Recovery.
Palmer and Taft[27] (Case 2)	25	R	?	Recovery.
Milhorat[24]	21	L	2400 cc.	Recovery. Transfused for anemia.
Housden and Piggot[15]	44	L	None	Fatal. Ruptured bleb and torn adhesion found.
Kjaergaard[19] (Case 1)	20	L	400 cc.	Recovery. Air injected on 5 occasions.
Kjaergaard[19] (Case 2)	25	L	"Few squirts of of blood"	Recovery.
Woll[38]	43	R	"Several times"	Recovery.
Leggett, *et al.*[22]	?	?	"A specimen of fluid"	Recovery.
Bellon[3]	21	R	"Three times"	Recovery.
Staffieri[23]	24	R	Thor.	Recovery.
Frey[12]	30	R	1220 cc.	Recovery.
Castex and Mazzei[7]	35	R	?	Recovery.
Holden[16] (Case 2)	25	R	"Small amount"	Recovery.
Aguilar and Ferradas[1] (Case 1)	37	L	200 cc.	Recovery.
Aguilar and Ferradas[1] (Case 2)	29	L	200 cc.	Recovery.
Wilson[37] (Case 1)	31	L	2745 cc.	Recovery.
Catuogno[8] (Case 1)	27	R	200 cc.	Recovery.
Catuogno[8] (Case 2)	27	R	500 cc.	Recovery.
Centeno, *et al.*[9]	27	R	Thor.	Recovery.
Jones and Gilbert[17]	23	R	2000 cc.	Fatal. Fluid replaced by air. Fibrin masses found at autopsy.
Korol[20] (Case 1)	35	R	35 cc. plus air	Recovery. Developed empyema; tube drainage for 6 weeks.
Korol[20] (Case 3)	?	L	3900 cc.	Recovery. Previous pleural effusion.
Korol[20] (Case 4)	33	L	Aspirated 18 times	Recovery.
Hopkins (Case 1)	30	L	2800 cc.	Recovery.
Hopkins (Case 2)	30	L	120 cc.	Recovery. Only reported case in a woman.
Hopkins (Case 3)	30	L	200 cc.	Recovery

* Thor. = thoracentesis; amount removed not stated.

Case Reports. CASE 1.—A colored male, aged 30, was in good health until August 26, 1934, when he contracted an acute respiratory infection. While eating dinner on September 2, he choked on a piece of meat and coughed several times. After dinner he became aware of dull discomfort in the upper part of the left side of the chest. Within an hour the pain became more severe, and spread downward as far as the costal margin; it was definitely related to respiration. The pain grew worse and dyspnea increased; he was referred to this hospital the following evening. On admission there was obvious dyspnea, but no cyanosis was noted. The respiratory rate was 32 per minute and the pulse rate 132. The blood pressure was 114 systolic, 80 diastolic. Examination of the chest showed typical signs of a complete left-sided pneumothorax, with possibly a slight amount of effusion. The heart and mediastinum were shifted to the right. The right border of the area of cardiac dullness was found to be 12 cm. to the right of the midsternal line; the left border was apparently under the sternum. There was a soft systolic murmur heard over the body of the heart. The findings on physical examination were otherwise unimportant.

On the following morning, the patient showed extreme dyspnea. There were physical signs of an effusion extending upward as high as the angle of the scapula. A roentgenogram confirmed the presence of a complete pneumothorax with pleuritic fluid (Fig. 1). The blood pressure had fallen to 94 systolic, 70 diastolic. Thoracentesis was performed to relieve the respiratory distress. The intrathoracic pressure was +4 cm. of water. Air (1600 cc.) was removed; bloody fluid then appeared and 80 cc. of this was allowed to flow out before the needle was withdrawn. There was an astonishing improvement in the condition of the patient. His respiratory difficulty practically disappeared and during the day his blood pressure rose to 118 systolic, 82 diastolic. A blood count that day showed 4,300,000 erythrocytes; the hemoglobin was 90%. The pleural fluid had a hemoglobin content of 80%, indicating that it was largely blood.

The clinical condition of the patient remained good, but there was a gradual increase in the amount of pleural fluid. This eventually resulted in the return of dyspnea, and subsequent aspirations were performed to relieve him. During the next month, thoracentesis was performed on four occasions, with the removal of a total of 2800 cc. of fluid. The hemoglobin content of the fluid decreased progressively from 80% to a point where an accurate determination was impossible on the last specimen. If calculated on the basis of 100% hemoglobin, there was removed a total of 1250 cc. of blood in the 2800 cc. of fluid. During this time, the blood hemoglobin fell from 90 to 63%.

Repeated sputum studies were negative for tubercle bacilli. Guinea-pigs were inoculated with the fluid obtained by aspiration; they failed to show any signs of tuberculosis. The patient's lung gradually reëxpanded. He was discharged 7 weeks after admission with no clinical or Roentgen evidence of pneumothorax, and only a very slight amount of pleural fluid, which subsequently disappeared entirely. He has been followed for 2 years without any evidence of pulmonary tuberculosis or other lung disease. He has gained weight, is working regularly, and has had no further symptoms referable to the lungs.

CASE 2.—A white woman, aged 30, had not felt well during the preceding year, but was never ill enough to lose time from her work—a clerical position. On August 20, 1935, she developed malaise, chilliness, fever, and some cough. She remained in bed for one day. On August 24, she felt a sudden sharp pain over the left side of the thorax; this persisted. She did not recall any previous strain or cough. She was admitted to the hospital 5 days after the onset of this pain.

The physical examination showed signs suggesting a partial pneumothorax on the left. A roentgenogram confirmed this and also showed the presence of a small amount of fluid. Although dyspnea was not trouble-

some, an exploratory thoracentesis was done. After 150 cc. of air had been removed, blood appeared; 120 cc. of this was removed. Unfortunately no cell count or hemoglobin determination was done on this fluid, but a smear showed that it contained a moderate number of intact erythrocytes and a large number of degenerating cells from which the hemoglobin had disappeared. No further aspirations were performed.

Under conservative treatment, the patient improved rapidly. Within 3 weeks the lung had completely reëxpanded and the fluid had disappeared. Repeated sputum studies were negative for tubercle bacilli; guinea pig inoculations were also negative. Serial roentgenograms over a period of 11 months have failed to demonstrate any evidence of a tuberculous lesion in the lung. The patient is able to carry on her regular duties without discomfort.

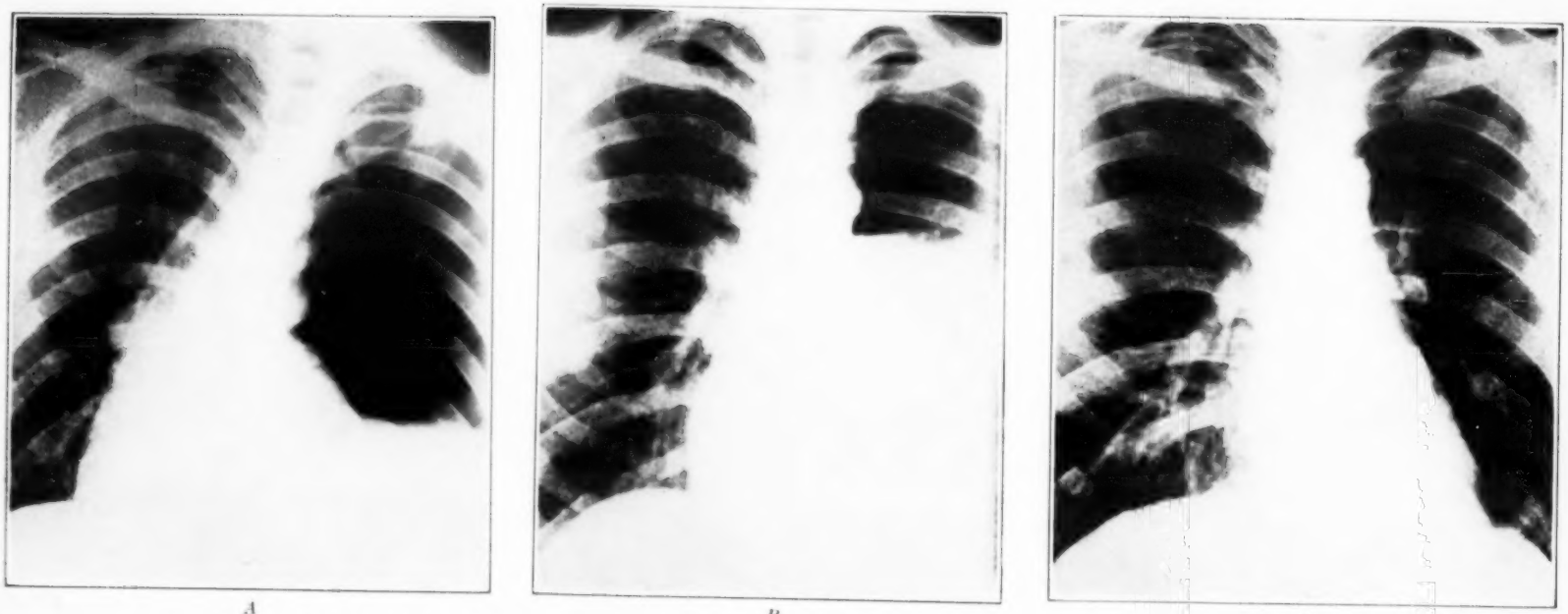
CASE 3.—A white male, aged 30, although never robust, had never been seriously ill. Several years ago, he had had an attack of sharp pain over the left side of the thorax; this had lasted only a few hours and had never recurred. He remembered no further details concerning it. On the afternoon of February 13, 1936, while shaving, he felt a sudden, severe, very sharp pain in the region of the base of the left lung. Within 15 minutes, the pain had spread upward to the shoulder and backward to the lumbar region. It was definitely aggravated by deep respiration. During the next half hour, the pain seemed to decrease somewhat and a short time later he reported for work at the restaurant where he was employed as night manager. The pain recurred and gradually became more severe. At 9 P.M. it suddenly became very severe and he collapsed but did not lose consciousness. He vomited once, and passed the night in a chair, because of dyspnea. The following morning a physician strapped the left side of the chest; this afforded some relief. However, the pain continued and gradually became most severe over the left lower quadrant of the abdomen. He was admitted to the hospital that evening, about 30 hours after the onset of symptoms.

Physical examination showed a dyspneic young man in obvious distress. The blood pressure was 108 systolic, 65 diastolic. The pulse rate was 108 per minute and the respiratory rate 30. There were typical physical signs of hydropneumothorax on the left side. The heart was apparently displaced somewhat to the right. A fluoroscopic examination confirmed the diagnosis. The films showed some irregularity at the apex of the partially collapsed left lung, suggesting a possible adhesion. On February 17, thoracentesis yielded air and 200 cc. of bloody fluid which did not clot. A cell count on this fluid showed 4,500,000 erythrocytes per c.mm.

The patient remained fairly comfortable. Physical examination and fluoroscopic studies showed that the amount of fluid was decreasing, so no further aspirations were attempted. On February 26, there was still a small pleural collection, but the pneumothorax had largely disappeared. Films showed that the right lung was clear. The upper portion of the left lung appeared normal; there were no gross lesions seen in the lower portion, but detail was somewhat obscured by the remaining fluid.

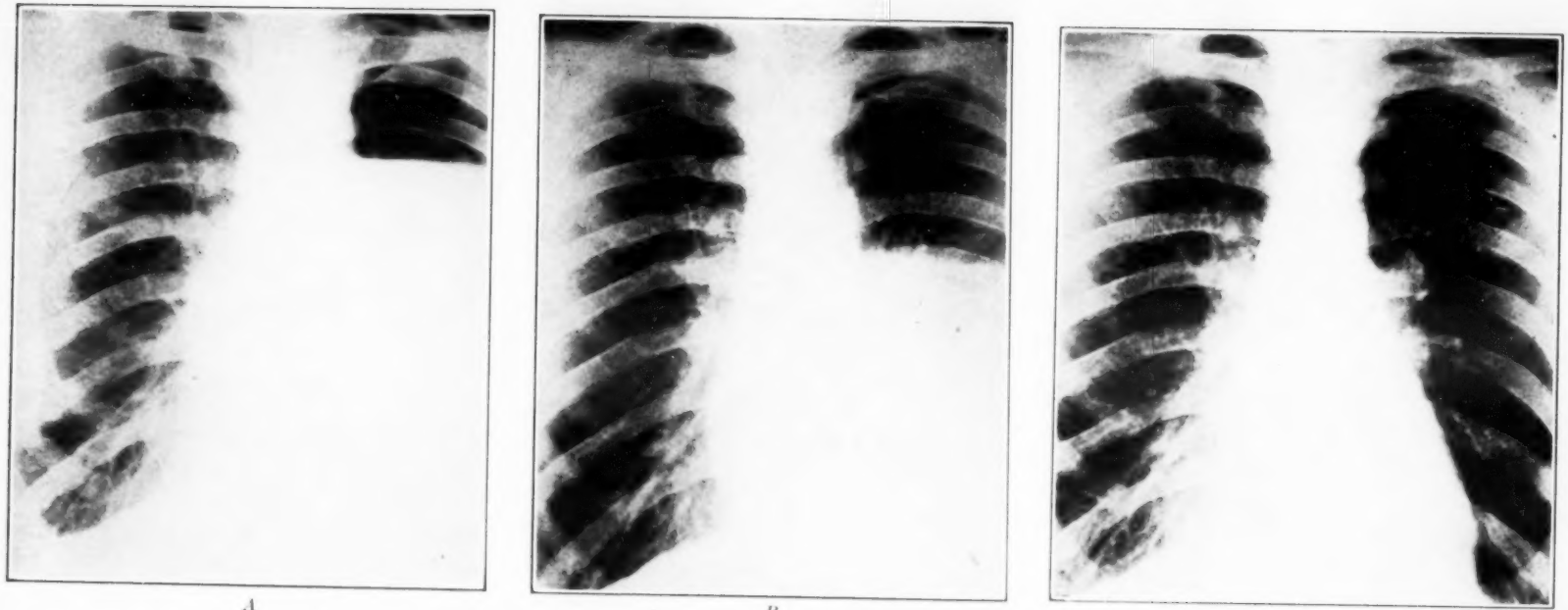
Repeated sputum studies were negative for tubercle bacilli. Smears and cultures of the pleural fluid were negative. Guinea pigs were inoculated; they failed to develop any signs of tuberculosis. During the past 6 months he has had no further symptoms referable to the lungs, and he appears to be in excellent health. The roentgenograms are normal (Fig. 2).

Historical Survey. Although Pitt[29] is usually given credit for calling attention to this condition in 1900, and for giving to it the present-day name of spontaneous hemopneumothorax, there are earlier reports of cases that were apparently of the same type.



A B C

FIG. 1.—Case 1. (*A*) On admission. (*B*) After removal of 1600 cc. of air and 80 cc. of blood. (*C*) Appearance 7 weeks later.



A B C

FIG. 2.—Case 3. (*A*) On admission. (*B*) After removal of air and 200 cc. of fluid. (*C*) Appearance 5 weeks later.

Laennec[21] described this condition, although he incorrectly attributed the presence of air in the pleural cavity to the fact that "the blood is sometimes decomposed and an aëriform fluid is disengaged, producing particular symptoms, as we shall see more particularly in the chapter on Pneumothorax." Later, he referred to an autopsy, in the course of which "upon penetrating the left side of the chest, a large quantity of inodorous gas made its escape with a hissing sound." The pleural cavity contained "about ten ounces of a bloody serosity." He also referred to the earlier report of Littré. From that time onward, there appear occasional reports giving fairly typical descriptions of this symptom complex, often under the misleading title of hemorrhagic pleurisy.

With the development of roentgenography, the definite demonstration of air and fluid in the pleural cavity became easier and more common. During the first two decades of this century, 7 definite cases of this condition were reported. During the past 15 years there has been an increasing amount of interest in this subject, and many additional reports have appeared (Table 1).

Aspiration for the relief of dyspnea in this condition was successfully used in this country by Whittaker[35] in 1876. He removed 34 ounces of bloody fluid and air from a chest, and was delighted to note the prompt improvement in the condition of the patient, who subsequently recovered without further complications.

Etiology. These cases can be divided into two groups. The first would include those which occur in persons who have tuberculosis; the second—a much larger group—those without demonstrable tuberculosis. In 2 of the fatal cases there had been rupture of a tuberculous lesion giving rise to an opening from the lung into the pleural cavity. In 6 of the patients who survived, subsequent examinations showed definite or suggestive evidence of tuberculosis. In these cases, one may postulate an etiology similar to that in the fatal cases. Three typical cases occurred in patients who were receiving therapeutic pneumothorax for known tuberculosis, presumably as a result of the tearing of adhesions containing lung tissue and blood-vessels, or from rupture of a caseous tuberculous focus.

In the majority of cases, tuberculosis could not be demonstrated. These represent merely spontaneous pneumothorax with bleeding as a complicating factor. The etiology of spontaneous pneumothorax is unsettled, but the evidence is accumulating to prove that in very many cases it is not due to tuberculosis. In his monograph on the subject, Kjaergaard[19] reported follow-up studies on 49 cases. These patients were reëxamined at intervals ranging from 3 to 18 years after the initial pneumothorax. In only 1 case was there clinical or roentgenographic evidence of pulmonary tuberculosis. He also reviewed the cases reported in the literature. In 6 instances there had been found at autopsy superficial air vesicles at the pleural surface of lungs otherwise healthy. Microscopic examina-

tion showed that there was often a valve-like piece of tissue which would lead to a gradual increase in the pressure within the vesicle, and its eventual rupture. Roentgenologically, he was able to demonstrate such a vesicle on the surface of the lung in 1 patient, and a similar finding has been reported in hemopneumothorax by Castex and Mazzei,[7] and by Korol.[20] Housden and Piggott[15] found 2 subpleural blebs in their fatal case. This type of lesion could easily be missed unless roentgenograms were taken in various planes. Kjaergaard's conclusion was that spontaneous pneumothorax was usually a benign process, probably due to rupture of such vesicles, and rarely due to demonstrable tuberculosis.

If we accept this view, two possible sources of hemorrhage are apparent. A vessel in the wall of the ruptured vesicle may be torn, leading to a gradual accumulation of blood in the pleural cavity. In the autopsied cases, however, the walls of these vesicles have been very thin and have shown only small vessels. A more probable explanation is that the collapsing lung tears pleural adhesions containing blood-vessels; this has been proved in some of the autopsied cases. The occurrence of such adhesions is fairly common, as shown by Leopold and Lieberman.[23] They report that at autopsy adhesions were found in almost 50% of all persons above the age of 20, even after eliminating all cases with a history of acute or chronic pulmonary disease. In many cases these adhesions contain large blood-vessels. Rupture of adhesions with hemorrhage is one of the recognized complications of therapeutic pneumothorax, and the same thing undoubtedly occurs in spontaneous pneumothorax. The degree of elasticity of the adhesions determines the amount of collapse which may exist before such a rupture occurs. This explains the fact that in some patients the signs of hemorrhage appear early, while in others there is definite evidence to show that the bleeding does not begin until several hours after the initial pain and the appearance of signs of pneumothorax.

Symptomatology. This accident occurs most frequently in patients who have previously been in good health. The initial pain may occur while the individual is at rest, or it may appear on slight exertion. In many instances it is preceded by cough, sneezing, laughing, yawning, hiccough, straining or some other procedure that would suddenly alter the intrapleural pressure. The pain is usually localized at the onset, but later it may spread to involve one entire side of the chest, and in some instances it radiates to the abdomen also. Dyspnea may be slight or extreme. It appears after a variable length of time, depending upon the rate at which air enters the pleural cavity. When there is a valve-like opening, a high positive pressure with displacement of the mediastinum may develop. In many of the cases there has been noted a second sharp attack of pain occurring at any time from a few hours to several days after the original pain. Following this, signs of effusion

appear. The initial pain represents the onset of the pneumothorax; the second attack of sharp pain is due to the tearing of an adhesion. If the bleeding is slow, systemic signs of hemorrhage may not appear for hours or days, or may never appear. In several of the recorded cases the presence of blood has been discovered during a Roentgen examination or as an unexpected finding in the course of thoracentesis for the relief of dyspnea due to the accumulated air. In other patients the bleeding is more rapid and the signs of internal hemorrhage appear early in the course of the disease. In such cases, the physical signs of fluid in the pleural cavity are usually definite, and may even obscure the presence of air. In a few instances, the obvious signs of shock and internal hemorrhage, associated with pain which spreads to the upper abdomen, have led to a tentative diagnosis of an acute surgical lesion of the abdomen. Fortunately the correct diagnosis has usually been made before subjecting these patients to a laparotomy, but in one instance[11] the error was not discovered until after operation.

Treatment. No uniform treatment can be outlined; each case requires individual consideration. Control of the bleeding and treatment of shock are the emergencies which must first be met. These demand absolute rest, with the liberal use of sedatives if necessary. Roentgen examinations should be postponed for several days, unless portable equipment is available. Relief of dyspnea comes next. An oxygen tent may suffice.[34] If dyspnea is severe and persistent, it may be necessary to allow the escape of some air or fluid; this can be done most safely with a pneumothorax apparatus. No attempt should be made to continue the aspiration to the point of producing a negative pressure. The value of pneumothorax in controlling pulmonary hemorrhage in tuberculosis is well known, and a high intrapleural pressure with a collapsed lung should promote hemostasis in these cases also. A large transfusion or the intravenous injection of fluid carries with it the danger of raising the blood pressure and prolonging the bleeding. Small transfusions are justifiable in an effort to promote clotting, or if the anemia becomes extreme. Blood aspirated from the pleural cavity has been injected into the patient's vein,[17] but this procedure is not recommended as a routine measure. The intramuscular injection of whole blood is a harmless procedure, and although it has not been tried in these cases, there is evidence to show that it has a definite hemostatic action. Several authors have suggested that if bleeding persists, a thoracoscopy or thoracotomy might be performed in an attempt to locate and treat directly the bleeding point. Such a procedure would be of doubtful value; in 2 of the fatal cases,[18,30] the authors have been unable to locate the site of bleeding even at the autopsy table.

If the patient survives the first critical stage and the bleeding ceases, the question arises as to whether or not the blood should be

aspirated. A survey of the literature shows that the patients who were not subjected to repeated aspirations seem to have done as well as those who were tapped repeatedly. It has long been known that blood in the pleural cavity shows little tendency to clot. Pagenstecher[26] showed that blood which had remained in the pleural cavity for 6 hours had lost its power to clot; this observation has been confirmed repeatedly. He believed that the pleura exerted some protective action, and compared it to the vascular endothelium in its ability to maintain blood in a fluid state. Recently it has been claimed that respiration acts mechanically to defibrinate the blood, and that the fibrin is deposited on the diaphragm and pleura. Jones and Gilbert[17] attribute the fatal outcome in their case to the formation of fibrin masses which eventually caused circulatory failure. In other cases which have come to autopsy such massive deposits of fibrin have not been recorded. If repeated aspirations are carried out, they should not be done with the hope of preventing this complication; Pagenstecher's work would indicate that if defibrination occurs, it takes place rapidly and is complete before one could be certain that active bleeding had ceased.

Blood in the pleural cavity is slowly absorbed. If the amount is small, it is justifiable to delay thoracentesis for at least a week or two. If there is evidence that the amount of fluid is decreasing, nothing need be done. If it has not decreased appreciably, it should be withdrawn. If fluid is present in large amounts it may give rise mechanically to pressure symptoms which are sufficient to justify its early removal. In several instances,[37,19,17,10,16] air or nitrogen has been injected into the pleural cavity as the blood was removed, to maintain compression of the lung and to minimize any tendency toward recurrence of the bleeding. This should always be done when any considerable amount of fluid is removed. It has been claimed that calcification of the pleura may result if the blood is not completely aspirated; this complication has not been reported in any of the cases reviewed, but as it is a process which may require years to develop, it may be reported later.

The patient should remain under observation for months after his apparent recovery. Although recurrent spontaneous pneumothorax is well known, there are no recorded cases of recurrence of hemopneumothorax. It is probable that the fibrin deposits, or the presence of blood in the pleural cavity with a resulting sterile pleurisy, leads eventually to the formation of such extensive pleural adhesions that subsequent collapse and bleeding become impossible.

Age, Sex and Side Involved. An examination of Table 1 shows that this is predominantly a disease of early adult life. Of 44 cases in which the age is stated, 26 occurred between the ages of 20 and 30, and 16 between the ages of 31 and 40. This corresponds with the usual age of most strenuous physical exertion, but exercise does not seem to be immediately concerned with the onset of symptoms.

The overwhelming proportion of cases in males is difficult to explain. If these abnormal air vesicles are the result of developmental defects, one would expect to find them in females as frequently as in males. If latent tuberculosis plays any part, one might expect a higher incidence in women. If physical exertion is of importance in the development of the predisposing factors, one would expect that with the entrance of girls and women into strenuous types of sport and work there would appear an increasing number of cases in this sex. No known explanation on an endocrine basis has been advanced.

The side involved is apparently a matter of chance; each side has been involved in approximately the same number of cases.

Summary and Conclusions. Three cases of spontaneous hemopneumothorax are described, including the first recorded instance of this condition in a woman. Forty-six cases reported since 1900 are briefly summarized.

A majority of the cases have occurred in persons who had no demonstrable pulmonary tuberculosis or other disease of the lungs. The etiology of this condition is not proved, but it is probably due to the rupture of an emphysematous subpleural air vesicle, followed by the tearing of preëxisting pleural adhesions which contain blood-vessels.

During the first 48 hours, aspiration is justifiable for the control of dyspnea but not as a routine measure. When the bleeding has stopped, the fluid should be removed and replaced by air.

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OIL OF WINTERGREEN (METHYL SALICYLATE) POISONING.

REPORT OF THREE CASES, ONE WITH AUTOPSY, AND A REVIEW OF THE LITERATURE.

BY CHARLES S. STEVENSON, M.D.,
ASSISTANT IN PATHOLOGY, JOHNS HOPKINS UNIVERSITY,
BALTIMORE, MD.

(From the Department of Pathology of the Johns Hopkins University.)

As is shown by the literature, poisoning by oil of wintergreen is of rare occurrence, but its apparently increasing frequency and the circumstances under which it occurs make it of especial interest. The subject was brought to the author's attention by a case upon which he recently performed an autopsy. The purpose of this paper is to report 3 new cases, including 1 fatal case with autopsy,* and to reiterate the fact that oil of wintergreen is a deadly poison and should officially be publicized as such. The reports of 43 cases were culled from the literature, of which 13 included necropsy findings.

The mortality of the whole series was 59%; 41% occurred in infants, all of whom drank oil of wintergreen from a bottle left within their reach by unsuspecting parents, who were astounded to find out that the substance which they used as a liniment was a potent poison. In 2 instances the liniment was drunk by inebriated adult chronic alcoholics evidently craving something stronger than whiskey.[49, 65] In France and Germany, the bottles are usually marked either "For external use only" or "Poison," and 4[4, 11, 34, 62] of the 5 cases found in the French literature were deliberate suicides. One woman[51] took the substance hoping to produce abortion. It has been reported that native African women in some isolated tribes in Northern Rhodesia commit suicide by filling their vaginas with powdered bark from the root of a native species of milkwort, and an analysis of this bark has shown it to contain a considerable quantity of methyl salicylate.[62] In the remaining 86% of this series, the poisoning was accidental.

The earliest cases on record are to be found in the 1832 edition of T. R. Beck's "Elements of Medical Jurisprudence," and are likewise repeated in the later edition;[6] 55% of the cases have occurred during the past 16 years and are spread out rather evenly over this period (Table 1).

* From the Harriet Lane Home of the Johns Hopkins Hospital.

Of the 4 cases in the files of the Harriet Lane Home, 1 has been reported.[50] The others are presented briefly below, all inconsiderable negative findings being omitted.

Case Histories. CASE 1.—W. B., (H.L.H. 54742), male, white, aged 2 years. *Past history:* non-contributory. *Present illness:* One morning, September 23, 1927, the infant drank about 15 cc. of oil of wintergreen. He vomited one-half hour later, and the vomitus smelled strongly of the drug. He continued to vomit all day, asked for water and vomited it. However he did not vomit for 6 hours during that night. Six hours after taking the poison he began to breathe deeply and this symptom increased during the night and the next morning, when he was also found to be deeply cyanotic and his urine showed 4+ acetone and salicylate tests. Because of the hyperpnea and cyanosis, his father, a doctor, brought him to the hospital.

Physical examination: (3 P.M., September 24, 1927, 29 hours after taking the poison). Temperature 104° F., pulse 180, respirations 60, blood pressure 105/60. The child was well developed and nourished and was prostrated. He lay limply in the arms of his mother and responded only slightly. His skin was generally cyanotic, with a marked pallor about the nose and mouth; the corners of the mouth twitched occasionally. The respirations were rapid and deep, of typical air-hunger type. The pulse was weak and rapid, but regular. The eyes showed contracted pupils, injection of the conjunctivæ, and a tendency for them to roll upward under half-closed lids. The mouth was dry and the buccal mucous membranes were not injected. The breath was acidotic. The heart sounds were of poor quality. The abdomen was moderately distended but not tender. The tendon reflexes of the arms and legs were hyperactive.

Urinalysis: Specific gravity 1.022, acid reaction, sugar 0, albumin trace, acetone 5+, diacetic acid and salicylate ($FeCl_3$ test) 5+. Microscopic examination: occasional red blood cells. Blood chemistry: CO_2 combining power 24.9 vols. %.

Treatment and Course: On admission the child was given caffeine and adrenalin, and the stomach was lavaged with 6% sodium bicarbonate, 2 gm. of the salt being put through the tube and left in the stomach; 100 cc. of 5% glucose was given intravenously, followed by a transfusion of 300 cc. of whole citrated blood. The color and pulse improved but hyperpnea persisted and the cheeks became flushed. By night on the day of admission the respirations had slowed up slightly but still remained deep. The child drank 5% glucose thirstily, and was given 1.2 gm. of sodium bicarbonate every 3 hours. Later on, there was evidence of excess mucus in the throat and 0.13 mg. of atropine was given with beneficial effect. Late the first night in the hospital the child refused to drink fluids. To counteract this, 75 cc. of a mixture of equal parts 5% sodium bicarbonate and 5% glucose was given per rectum every 3 hours, preceded each time by a soft soap enema. Early the next morning he received 300 cc. 5% glucose intrasinously, preceded by 3 mg. morphine. By morning (September 25, 1927), the child was brighter and responded to his name; pulse 160 and better quality, temperature 102.8° F., respirations 48 and deep, cyanosis marked. At noon he was given a 250 cc. blood transfusion with 100 cc. normal saline. After this his blood pressure was 95/60. That night there were signs of pneumonia at both bases and his pulse was 180 and weak. Digifoline was given, 1 ampule every 3 hours for 5 doses. The next morning, 72 hours after taking the poison, the child was greatly improved; pulse 120 and good quality, cyanosis less, and respirations less deep and rapid. The temperature was 100.6°, and the lung signs were less marked. The infant asked for food.

TABLE 1.—METHYL SALICYLATE POISONING.

Author.	Date.	Sex.	Age.	Dose in cc.	Symptoms and signs.														Blood studies.					Urinalysis.			Outcome.		Treatment and remarks.
					Minutes elapsed before symptoms appeared.	Vomiting.	Abdominal pain (burning).	Rapid respirations.	Deep (Kussmaul) respirations.	Rapid pulse.	Marked cyanosis (terminal or early).	Flushed skin.	Extreme thirst.	Stupor and coma.	Convulsions.	Impaired hearing or tinnitus.	Dimness of vision.	Temperature when first seen.	Leukocytes (thousands per cu.mm.)	Hemoglobin in %.	CO_2 combining power (in vol. %).	Non-protein nitrogen.	Sugar.	Salicylate.	Acetone.	Albumin.	Recovered.	Hours after ingestion elapsing before death.	
Beck[6]	?	M	6 adults	?	..	+																					Yes		6 soldiers drank "tea" with m. salic. flavoring.
Beck[6]	1832	M	?	30																							No	?	No treatment.
Gallager[15]	1852	M	9 yrs.	16		+	+	+	+	+		+	+			+											Yes		Calomel, phlebotomy. Delirious, very hungry.
Jewett[31]	1867	F	55 yrs.	15		+	+	+		+		+	+	+			+										No	?	No treatment. Early failure of sight and hearing.
Hamilton[19]	1875	F	Adult	16		+		+		+		+		+	+	+	+										Yes		No treatment. Developed left hemiparesis.
Ott (reported by S. V. Able[1])	1885	M	30 yrs.	250	30	+		+	+	+		+		+		+											No	17	Alkalis; purgatives which did not act.
Haldermann[17]	1886	F	29 mos.	12	? 1	+	+			+			+	+	+												No	18.5	Seen by doctor 20 min. before death.
Pinkham* [51]	1887	F	25 yrs.	30		+	+	+		+		+		+	+	+	+										No	15	No treatment. Took m. salic. to produce abortion.
Stillé[59]		M	9 yrs.	15		+		+		+																	Yes		No treatment.
Van Wagenen[61]	1900	M	2 yrs.	5	360	+	+	+	+	+				+	+			97									No	48	Emetics, cathartics, eggs and milk 7 hrs. after poisoning.
Pillsbury[48]	1900	M	Adult	60	120	−	+			+		+															No	25	Persistent diarrhea and sweating. Emetics ineffectual.
Price and L'Engle[42]	1903	F	2 yrs.	4	120	+	+	+	+	+		+	+	+	+	+	+	98.6						+			No	10	Persistent diarrhea. Respiratory failure and death.
McNerthey[39]	1903	M	3 yrs.	12	180	−	+	+		+		+	+		+												No	?	No treatment.
Baum[5]	1903		28 yrs.	24													+										Yes		No treatment.
Mann and Brend[38]	1914		3 yrs.	12			+								+												No	?	No treatment.
Rosenbloom and Johnston[54]	1918	M	40 yrs.	30	20	+	+			+						+		98.6						+	+	+	Yes		Recovery in 7 days. Glucose and alk. proctoclysis.
Meyers[42]	1920	M	2 yrs.	30	60	+	+	+	+	+		+		+		+‡		98.6						+	+4	−	Yes		Alkalis.
Howard[28]	1921	M	21 yrs.	6		+									+												Yes		Both drank oil of wintergreen with ginger ale at a dance; 1 died later "that night," the other recovered.
Howard[28]	1921	M	21 yrs.	6		+									+												No	?	

Legrain and Badonnel[* 34]	1922	F	Adult	60	600	+				+			+	+											No	18	Immediate gavage. Terminal "collapse."
Wetzel and Nourse[* 62]	1925	?	21 mos.	10	240	+		+	+	+	+	+		+	+								+	+	+	No	36	Morphine and bromides. Term. sudden pulmonary edema.
Olmsted and Aldrich[46]	1925	?	4 yrs.	?	120	+	+	+	+	+		+	+	+				99.2			33.4		130	+4	+4	−	Yes		Alkalis.
Archambaud and Friedmann[3]	1926	F	17 yrs.	30	360	+	+	+	+	+	+		+	+				100						+4		Trace	No	34	Cardiac stim. and diuretic; alkalis. Respiratory collapse.
Lathrop[* 33]	1926	M	19 mos.	?–8	15	+		+	+		+	−		+	+						33.2				−		No	19.5	Gavage, soda bicarb. orally and rectally; O_2. Resp. failure.
Olmsted and Aldrich[46]	1927	?	2.5 yrs.	?		+	+	+	+	+		+	+	+	+			100	7.2	80	37.6		170	+3	+3		Yes		Alaklis.
Pincus and Handley[50] H.L.H. 46664	1927	M	2 yrs.	? 30	5	+		+	+	+	+	+		+	+			99.6	25.6	83	35.0	62	145				No	14	No treatment.
Arnold and Jacobsen[* 2]	1927	M	10 mos.	10	45	+		+	+	+		+		+	+		±	105						+	+4	+	No	16.5	Rectal glucose and alkali, intraven. glucose. Marked hyperpnea.
Woodbury and Nicholls[* 65]	1927	M	25 yrs.	?		+																		+		−	No		Sudden death. Chronic alcoholic.
Woodbury and Nicholls[* 65]	1927	M	22 mos.	?	180	+									+									+			No	17	Morphine; ca. lactate, brandy, and bismuth.
Meyerhoff[* 41]	1929	M	22 mos.	24	?1	+		+		+	+		+					100	10.3	63					*anuria*		No	24	Mag. sulph. by mouth. Caffeine and atropine. Alk. proctocly.
Sevringhaus and Meyer[67]	1930	F	Adult	30	240	+		−		−						+		98.6					148		+	+	Yes		Forced fluids. **Had glycosuria.**
Bauby and Fromont[* 4]	1930	M	26 yrs.	80	120	+		+	+	+		+	+	+			+										No	19	No treatment given. **Had marked mydriasis.**
Hughes[* 39]	1932	M	17 mos.	4	? 1	+		+		+	+	+		+	−			100									No	12	Emetics immediately. **Terminal** resp. failure.
Pincoffs and Chambers[49]	1932	M	49 yrs.	45	30	+		+	+					+					11.7	80	28.8	79	167	+	+3	+2	Yes		Gavage, alkali-glucose proctoclyses. Died pneum. later.
Pincoffs and Chambers[49]	1932	M	21 mos.	?	? 1	+		+	+	+	+	+		+				102	23.8		24						No	23	Immediate gavage. Died in resp. failure.
Dwyer[* 12]	1933	F	15 mos.	8	60	+		+	+	+	+		+	+	+			98.6			36.5			+	+		No	13	Hypodermoclysis of sodium lactate, Ringer's sol.
Vleurinck and Bourguignon[* 63]	1933	F	Adult	?																							No	?	Vagina filled with milkwort bark. Suicidal intent.
Duvoir, Pollet, and Sainton[11 *]	1934	M	Adult	200	120	+	+	+	+	+								102						+		−	No	36	Gavage after 3 hrs.
Author's case, H.L.H 54742	1927	M	2 yrs.	15	30	+		+	+	+	+	−	+	−	−			104	8.0	85	24.9			+4	+4	Trace	Yes		Alkali and glucose sol. by mouth, rectum, vein. Transfusions.
Author's case, H.L.H. 67018	1930	F	22 mos.	?	? 1	+		+	+		−	−		+	−			100	10.0	65				+3	+3	−	Yes		Intravenous alkali and glucose solutions.
Author's case, H.L.H. 59309[*]	1935	F	1 mo.	5	30	+		+	+	+	−			+	−			105			41				*anuria*		No	23	Peppermint water and castor oil (home). O_2 at JHH.

* Reported autopsies.

Blood studies: hemoglobin 85%, white blood cell count 8000. No methemoglobin.

Urinalysis: albumin +, acetone 2+. Microscopic examination: a few red blood cells and hyaline casts.

The following day, September 27, 1927, the child was playful and well, but very weak. The respiratory rate was 38, the lungs were clear, and the urine showed only a faint trace of acetone and salicylate; the remaining convalescence was uneventful.

CASE 2.—J. M. (H.L.H. 67018), female, white, aged 22 months. *Past history:* non-contributory. *Present illness:* At noon, on May 10, 1930, the baby drank "one mouthful" of oil of wintergreen but immediately vomited it. She vomited everything she ate thereafter. Six hours following the poisoning, she began to breathe deeply, but did not complain of pain and was drowsy.

Physical examination: (3 A.M., May 11, 1930, 14 hours after ingestion of the poison). Temperature 100°. The child was well developed and apparently overnourished. The pulse was of good quality, and the respirations were rapid, deep, full and strong, being of typical air-hunger type. There was no cyanosis and the skin was of good color. The child lay stuporous until aroused and then resisted examination. The pupils were equal and reacted normally. The throat was markedly injected. The lungs were clear and the heart sounds normal. There was no abdominal distention. The deep reflexes were normally active.

Urinalysis: amber, 1.012, acid reaction, albumin 0, sugar 0, acetone 3+, diacetic acid and salicylate 3+. Microscopic examination: a few granular casts. Blood studies: Hemoglobin 65%, white blood cell count 10,000 (neutrophils 48%, lymphocytes 52%).

Treatment and Course. On admission she was given 250 cc. of equal parts 10% glucose and normal saline intravenously. About 8 hours later the hyperpnea was still marked and the child was sleeping deeply. She was then given 100 cc. 5% sodium bicarbonate and 100 cc. 5% glucose intravenously. This was repeated 6 hours later, and the child seemed greatly improved. At night, 33 hours after taking the poison, the child was practically well and the hyperpnea had all but disappeared. The next day she was well and the urine was negative except for a positive acetone test. On May 13, 1930 the urine was negative, and the following day the patient was discharged.

CASE 3.—A. C. (H.L.H. 59309), female, colored, aged 1 month, at 5 P.M., on November 4, 1935, was given 5 cc. of oil of wintergreen by an imbecilic child. Half an hour later the baby cried, choked and looked flushed, so the mother nursed her. The infant immediately vomited a white milky fluid which smelled strongly of wintergreen. Following this she seemed sleepy and refused breast and water. The mother noticed that the infant was "short of breath," but seemed very sleepy and did not cry. Two hours later the infant vomited again, the vomitus still smelling of wintergreen. At 9 P.M. a local doctor was called and he prescribed 5 cc. peppermint water every 3 hours. Soon after this, the mother gave 5 cc. castor oil and at midnight the infant had a copious stool, which also smelled strongly of wintergreen. She became more drowsy and hyperpneic through the night, and the next morning she "wouldn't wake up" and seemed "painful whenever touched." She had several more stools and voided a few times, and finally was brought to the hospital.

Physical examination. (1.30 P.M., November 5, 1935, 20½ hours after the poisoning). Temperature 105.6° F. The infant was comatose and occasionally lifted her legs up and cried feebly as though she had abdominal pain. Her respirations were very rapid and deep, of typical Kussmaul type. Her breath was acidotic. She was pale but not definitely cyanotic. The pupils

reacted to light and showed an intermittent, rapid, horizontal nystagmus. The lungs were clear, the pulse very rapid but of regular rhythm; the heart sounds were clear. The abdomen was soft and no masses were felt.

Blood studies: Wassermann reaction negative, blood culture sterile, CO_2 combining power 41 vols. %, total fixed base 167.6 cc./N/10.

Treatment and Course. The infant was given oxygen by mask immediately on her arrival at the hospital. Caffeine was given while preparations were made to administer intravenous fluids and a blood transfusion, but the baby died just as the fluids were begun, $23\frac{1}{2}$ hours after taking the poison.

Autopsy (No. 14495, 18 hours after death). The body weighed 4 kilos. and measured 54 cm. in length. The nutrition was average. The only lesions found macroscopically were a number of subpleural and subepicardial hemorrhages, some of which measured 8 by 4 mm. In the myocardium of the posterior wall of the left ventricle one small hemorrhage was found. There were small patches of edema in the lungs. The bladder was distended with 200 cc. of cloudy urine.

Microscopically, the sections showed little. In the lungs there were some areas of edema and hemorrhage but no distinct pneumonia. Some of the bronchioles in places had lost their epithelium and their walls contained neutrophils and eosinophils. A coagulum containing leukocytes and red blood cells was present in the lumen; a bacterial stain showed an occasional Gram-positive diplococcus, and these were not lancet-shaped. The sinusoids of some of the bronchial lymph nodes were engorged with old blood cells. No lesions were found in sections of the optic nerves, brain, spinal cord, kidneys, liver, spleen, pancreas, thymus, adrenals, heart, aorta, esophagus, stomach, intestines, costochondral junction of the rib, bladder, and mesenteric lymph nodes.

Anatomical Diagnosis. History of accidental methyl salicylate (oil of wintergreen) poisoning. Petechial hemorrhages in pleuræ and epicardium. Slight edema and hemorrhage of the lungs. Acute bronchitis (aspiration).

The 3 above cases and the case reported by Pincus and Handley[50] (Table 1) show a uniformity of symptoms and signs and present a definite clinical picture of this type of poisoning. All 4 of the infants vomited some oil of wintergreen shortly after taking it and vomited frequently thereafter. The deep and rapid respirations, found in each of these cases, came on after about 6 hours. The odor of oil of wintergreen was present in the stools and in the urine of 1 case.[50] Early cyanosis was found in the first of the new cases but in none of the other 3, while marked terminal cyanosis was seen in 1 of the 2 fatal cases. Two showed flushed cheeks while the other 2 were generally pale. An injected pharynx was seen in 1 case, while another showed bright red lips. All of the infants had sweetish breath (acetone?) and their blood CO_2 combining powers varied between 24.9 and 41 vol. % on admission. In 2 of these cases the conjunctival and scleral vessels were congested and the conjunctivæ injected; in 1 case the pupils were contracted, but in all they reacted to light. In each infant, the lungs were clear on admission, and while the pulse was fast, it was regular and usually of fair quality. In 1 case the abdomen was distended but in none was it tender. In 2 instances the tendon reflexes were hyperactive, while in 1, in which the baby had probably got very little poison and retained

only a fraction of this, they were normal. The infant seen after 20 hours was comatose; she had swallowed 5 cc. of the poison and was 1 month old. The one seen after 29 hours was semistuporous; she was 2 years old and had swallowed 15 cc. Another, seen after 14 hours, was "stuporous until aroused and then resisted examination;" she was 2 years old and had swallowed "about one mouthful" of the poison. Pincus and Handley's 2-year-old child "was able to sit and stand alone, though his actions were slow and deliberate," and he was seen at 10 hours and had taken an amount "not exceeding 60 cc." In all cases the temperature on admission was variable as was likewise the white blood cell count. The one infant which had a blood non-protein nitrogen determination showed it to be 62 mg./100 cc. Urine specimens were obtained on only 2 of these cases (both of whom recovered), and casts were found in both, while 1 of them (H.L.H 54742) showed a trace of albumin.

Pincus and Handley's case finally had convulsions and twitchings of muscles of the hands and face, while one of the above showed twitchings of the corners of the mouth. One infant showed a great thirst at times, which has been recorded as a frequent symptom. None have shown surgical shock, but in one the extremities were cold 8 hours after taking the poison and 6 hours before death.[50] Respiratory failure marked the terminus of the 2 fatal cases.

The case reported by Price and L'Engle[52] is of especial clinical interest in that they saw the child continuously from 1 hour after it had taken the poison until its death 9 hours later, and they do not report that it received any treatment other than gavage. They found that the child, a 2-year-old girl, had swallowed 4 cc. of commercial oil of wintergreen, and had vomited several times before coming to the hospital. On arrival at 9.30 A.M., she was still vomiting, but this ceased following the gavage. Examination showed a temperature of 98.6° F., pulse 100, regular and of good volume; respirations were 26 and regular.

The following quotation will best describe the clinical course:

"There was nothing abnormal in the child's appearance, and it showed no evidence of suffering pain. There were no further symptoms for 2 hours, when the patient seemed to have pain in the abdomen, was drowsy, and complained of great thirst. The pulse rate increased to 150 and within an hour the child's face became flushed, the respirations were somewhat labored and irregular, and there were evidences of impaired hearing and some hallucinations of vision. The temperature was not increased but there were slight twitchings of the hands and the muscles of the neck, and at this time delirium was first noticed. There was diarrhœa and a strong odor of oil of Gaultheria in the stools.

"At 3 P.M. the temperature was 99.4, pulse 132 and of good volume, respirations regular but somewhat labored. At 3.30 P.M., 7 hours after the drug had been taken, the child had a general convulsion, in which the arms and legs were extended, eyes rotated upward, head thrown back, neck rigid, but there was no arching of the back. The pupils were equal and were moderately dilated. This tonic spasm lasted about half a minute and

recurred at frequent intervals. The pulse was of fair volume but was slightly irregular, and the respirations were deep, labored, and gradually decreased in rate to 4 or 5 per minute. These symptoms increased until, finally, the child died of respiratory failure at 6.30 P.M., 10 hours after ingestion of the poison."

In Table 1 we find that the smallest lethal dose of the poison was 4 cc., and this occurred in 2 instances: One was in a 17-month-old infant who vomited it immediately,[29] and the other was a 2-year-old infant who had a persistent diarrhea.[52] The former was given emetics effectually but no other treatment, and died after 12 hours; the latter died in 10 hours, no treatment being given. The author's case (H.L.H. 59309), an infant of 1 month, swallowed about 5 cc. of the drug and vomited it a half hour later. It had no early treatment and died after 23 hours, shortly following its arrival at the hospital. Six cc., the smallest lethal dose in an adult, was taken in 2 instances,[28] in 1 of which the victim died after a few hours. Thirty cc. was lethal in 2 instances,[2,51] and they died 15 and 34 hours, respectively, after taking the poison. The former received no treatment. The latter received alkali fluids by mouth, a diuretic, and cardiac stimulants 10 hours after the poisoning; subcutaneous and intravenous lactate solution and subcutaneous oxygen were administered after 26 hours, when the patient had a sudden sinking spell.

The most rapid death occurred in 10 hours.[52] This was in an infant who took 4 cc. of the poison and who evidently received no treatment. Hughes' case[29] died in 12 hours and received emetics immediately after taking the poison. The most rapid death in an adult[51] was in 15 hours; she took 30 cc. and received no treatment. The average time before death in the infants was 21.3 hours, while in the adults it was 23.4 hours.

The most common symptom was vomiting, and it occurred in 87% of the cases; 33% had abdominal pain or burning. Rapid respirations and pulse were the most common signs, each occurring in 59% of the cases. In only 43% were deep respirations reported, and 35% of these recovered; 49% showed stupor and coma, of which 26% recovered; 40% had convulsions, with only 17% recovering, thus making convulsions the gravest prognostic sign. Flushed skin was found in 35% of the cases, and thirst in 26%. Cyanosis was found in only 22%. Tinnitus and dimness of vision occurred in 17% and 15% of the cases respectively. The temperatures given in the table are those taken when the patient was first seen by a doctor, which varied between 1 and 26 hours after the ingestion of the poison; it has been found that the temperature remains at 98.6° for about the first 6 hours. The blood counts were variable and apparently of no special prognostic value.

The lowest CO_2 combining power of the blood was 24 vol. %, and it was found in the infant reported by Pincoffs and Chambers.[49]

Despite treatment it died in 23 hours with terminal respiratory failure. The next lowest value for this blood property was 24.9 vol. %. It was found in one of the author's cases (H.L.H.54742), and, as was related above, this child recovered in about 80 hours. The average CO_2 combining power was 32.7 vol. %. Only two blood non-protein nitrogen determinations were found,[49,50] and these were 62 and 79 mg./100 cc. (of whole blood). The former was in an infant who died in 14 hours, and the latter in an adult who apparently recovered from the poison after 48 hours to develop pneumonia 2 days later and die of it in another week. The blood sugar readings have varied between 130 and 170 mg./100 cc. One case[57] is reported in which glycosuria was discovered and the blood sugar proved to be 148. Of the 5 instances in which it was reported, the average blood sugar was 152, and all but 1 of these patients recovered. Of the 15 reported tests for salicylates in the urine all were positive; 11 of the 12 tests for acetonuria were positive, while 7 out of the 12 cases tested showed albuminuria. Two of the cases, Meyerhoff's[41] and the author's (H.L.H. 59309) showed anuria. The bladder of the former, at autopsy, was practically empty, while that of the latter contained 200 cc. of urine.

The reports of 13 autopsies on cases of oil of wintergreen poisoning were found in the literature, and despite the fact that the terminology in some was indefinite and that the lesions described may well have been due to postmortem change, they, with the author's case, are briefly summarized in the following paragraph.

These patients died between 12 and 36 hours after taking the poison. Nearly half of the autopsies showed "generally engorged blood vessels," subepicardial hemorrhages, "congestion" of the gastro-intestinal tract, edema of the lungs, engorgement of the small vessels of the lungs, engorgement of the small vessels of the kidneys, and "cloudy swelling" of the renal tubule cells. The following conditions occurred in 30% of the cases; visceral subpleural hemorrhages, hemorrhages into the lung parenchyma and alveoli, "fatty degeneration" of liver cells, and lymphoid hyperplasia of the spleen. "Congestion" of the glomeruli, "fatty degeneration" of the tubules, and necrosis of the tubule cells were renal conditions found in 22% of the autopsies. Hyperplasia of the lymphoid tissue of the gastro-intestinal tract was reported in 3 cases,[3,41,63] but this condition was not found in the author's case.

None of the reports described the peculiar patchy marked inflammation and epithelial destruction of a few of the bronchioles found in the author's case. Since the infant was reported to be well before taking the drug and only a very few bacteria were found in the affected bronchi in the bacterial stains, it seems likely that the peculiar bronchitis may have been the result of aspiration of the drug.

Thus, there are no specific anatomic pathologic changes in these cases, and those which are found are fairly inconstant and do not present a picture which is typical in any way. Of greater importance are the physiologic pathologic changes, which will be reviewed in the summary of the pharmacologic investigations of the salicylates which follows.

In 1885, it was found[1] that the drug acts centrally in abolishing voluntary and reflex action and peripheral sensitivity; that with small doses of the drug the pulse is accelerated, the respiratory rate is increased, and the blood pressure is first depressed slightly and then increased, while, with large doses a permanent depression of all three occurs; that the ultimate fall of blood pressure is due to the poisoning effect of the drug on the heart and the peripheral vessels. The next year experimental evidence showed[64] that the drug has a direct effect upon the respiratory and cardiac "centers" in the medulla, and a recent article,[32] among other things, clearly bears out this fact.

The drug,[14,40] unless given in amounts much greater than the therapeutic dose, has no toxic effect upon the myocardium. Hoke[27] refers to the salicylates as being in the same class as histamine with regard to their property of paralyzing the smooth muscle of the small vessels, causing a marked dilatation of them. Methyl salicylate, given intravenously, apparently injures the capillary walls, especially in the lungs, where this injury results in the pulmonary edema frequently evidenced clinically and found anatomically at autopsy.[9,58,60]

The analgesic effect of small doses of acetyl salicylic acid is common knowledge and practice among laymen. The general toxic effects of sodium salicylate, acetyl salicylic acid, and methyl salicylate are the same and are due to the salicyl radical. The average oral dose of methyl salicylate U.S.P., is 0.75 cc. and 2 cc. is listed as the maximum dose. As has been stated, 4 cc. has been lethal in an infant, and 6 cc. in 2 adults. The toxic symptoms of dizziness, tinnitus, nausea, and vomiting are usually brought on by 2 to 3 cc. of the drug by mouth. The average toxic dose of methyl salicylate is two-thirds that of salicyl-salicylic acid and one-half that of sodium salicylate.[36] Commercial natural oil of wintergreen, of specific gravity 1.17, is 97% methyl salicylate and 3% terpene; commercial natural oil of birch is all methyl salicylate.[1] There is no difference in the toxicity and potency of the natural and synthetic forms of methyl salicylate.[58] Clinically, sodium salicylate and methyl salicylate poisonings are essentially similar.

Free salicylic acid in the stomach leads to nausea, burning, diarrhea and vomiting,[44] and these are believed by some to be due to the local irritation. In methyl salicylate poisoning, the epigastric burning is more intense than that of other salicylates.[29] It is also

thought by several writers [13,22a] that the salicylates have a central emetic action.

Small to moderate doses of sodium salicylate in animals and humans cause a slight diuresis;[7] full toxic doses a diminution of diuresis. This latter has been ascribed to both diaphoresis and diminished renal functional efficiency.[24,55] Further investigation,[21,25] showed that toxic doses of the salicylates in both normal and sick patients may cause not only some degree of anuria, retention of blood urea and non-protein nitrogen, a decrease in phenolsulphonephthalein excretion, and albuminuria, but also the appearance of white blood cells and hyaline casts in the urine. Eight cases gave clinical evidence of impaired renal function (albuminuria or increased blood non-protein nitrogen) (Table 1), and the thorough blood studies in the case of Pincus and Handley[50] show a retention of phosphate, a marked chloride retention, a decrease in total base, a marked increase in non-protein nitrogen, and an albumin-globulin ratio of 1 : 1. Unfortunately, permission for autopsy on this case could not be obtained; in the case which the author autopsied, no blood non-protein nitrogen or urea determinations were made and no urine obtained for study. However, in the autopsies thus far reported, there have been no definite anatomic pathologic lesions that correspond with the clinical evidences of renal functional impairment.

The antipyretic and diaphoretic property of the salicylates has been recognized and studied,[16,24] and was especially noticed clinically in some of the earlier cases of poisoning.[31,48,61] Only a very small amount (0.1% of dosage given) of salicyl is excreted in the sweat.[56b] The diaphoretic and vasodilatory action of these drugs are thought to be connected.

The esters of salicylic acid are absorbed by the skin more readily than the acid or its salt,[20] and the salicyl radicle has been detected in the urine 30 minutes after the skin application of oil of wintergreen.[35] Only the soluble sodium salicylate salts are absorbed in the stomach, and apparently no hydrolysis of methyl salicylate takes place there.[8] Very little hydrolysis of methyl salicylate takes place in the gastro-intestinal tract,[22b] and at autopsy, in 3 instances,[4,29,41] the "odor of the drug" has been noticed in the intestines, and, clinically, in the urine and stools in 2 cases (H.L.H 59309).[52] Thus, it seems probable that methyl salicylate is absorbed as such from the intestine. The salicyl radicle has been recovered from every body fluid and organ[20] following ingestion of methyl salicylate, but free salicylic acid has never been demonstrated in body fluids,[56a] and this is due to the fact that the average pH of the blood would not permit it.

Heat production is increased in salicylate poisoning, but, it is believed, through the dilated vessels and diaphoresis this heat is lost.[32] Nitrogenous metabolism is generally increased, and, in

patients given toxic doses of salicylate, the total nitrogen in the urine may show a 40% increase.[10] This is mainly due to increased uric acid excretion,[7] which is thought to be due to decreased uric acid catabolism in the blood.[18,53] The salicylates cause an increase in the blood lactic acid,[23,32] and in general also in blood amino-acids. Urinary ammonia is diminished,[45] and this fact points either to decreased deaminization or to impairment of renal function.

Glycosuria has been found in methyl salicylate poisoning.[57] Hyperglycemia, as can be seen in Table 1, occurred in all 5 cases where this determination was made.[46,49,50,57] Of the 12 cases examined for acetonuria, only 1 was negative, and of the rest, many gave a 4+ reaction.

Ingested sodium salicylate is recoverable from the urine to the extent of 80% in the form of a salicylate, and its excretion takes place over a period of 3 days.[20] On the other hand, ingested methyl salicylate is only 51% recoverable from the urine as the salicyl radicle, and its excretion is completed in 4 days. Of the methyl salicylate, 0.1% has been recovered still in its original form. To this relative retention of methyl salicylate is attributed its greater toxicity.[20]

The similarities of the symptoms of diabetic acidosis and salicylate poisoning have long been recognized, and Table 1 shows a markedly decreased blood alkali reserve (CO_2 combining power) in the 9 instances where this value has been reported. Despite evidence to the contrary,[43,56a] it is generally found that a decreased alkali reserve ("acidosis") does occur when toxic doses of the salicylates are given to animals and humans, and that it is not due to the products of fat metabolism alone, as in diabetes,[45] but also to the liberation or accumulation of other fixed acids in the blood.[32] There is thus usually a compensated fixed acid "acidosis."

In 6 of the cases listed no vomiting was reported (Table 1); of the 4 Harriet Lane Home cases, 1 infant (H.L.H 59309) vomited only twice, the others vomited more or less continuously for the first few hours. With regard to the effect upon the blood acid-base equilibrium of protracted vomiting, it is found that there is some divergence of opinion. Theoretically, a loss of HCl, due to vomiting, would produce an alkalosis. Actually, in children, vomiting is more often associated with an "acidosis"[47] in which, in severe cases, the intense air hunger, rapid pulse, dehydration and stuporous condition resembles that seen in the most advanced diabetes.[26] Studies on the blood serum show that the chlorides may not be lower than normal, that the base concentration (Na, K) may be subnormal, and that the alkali deficit appears to be due to the accumulation of large amounts of organic acids in the blood, the major portion of which are ketone acids, but with definitely more than the normal amount of lactic acid.[47] There seems to be no evidence that the vomiting actually causes acidosis.

To summarize, then, the lowered alkali reserve in the blood which is found in salicylate poisoning is contributed to by one or more of the following factors: 1, Impairment of renal function, as evidenced by retention of urea and non-protein nitrogen; 2, the presence of ketone bodies in the blood, as inferred from the acetonuria almost always occurring; 3, an increase in blood lactic acid; 4, an increase in blood amino-acids.

An attempt to correlate the symptoms and signs with the results of pharmacologic research shows that for the most part the vomiting, rapid respirations, rapid pulse, convulsions, impairment of hearing and vision, and the muscular twitchings are due to the effect of the drug on the central nervous system. The epigastric burning is caused by the direct irritating action of the oil on the gastric mucosa. The Kussmaul respirations, extreme thirst, stupor and coma, and to some extent the rapid pulse and convulsions are due to the acidosis. The marked cyanosis and flushed skin and, to some extent, the increased respirations and rapid pulse are the result of the dilatation of the peripheral blood vessels. Increased blood sugar and acetonuria are evidence of interference with the fat and carbohydrate metabolism.

The treatment, aside from gastric lavage, is symptomatic. The most remarkable recovery on record seems to be that of Case 1. Although this child, as was previously described, was not seen until 24 hours after taking the poison and was then *in extremis* and had a blood CO_2 combining power of 24.9 vol. %, albuminuria, red blood cells and casts in the urine, and a 5+ acetonuria, he recovered. His treatment, specifically, consisted of gastric lavage with 6% sodium bicarbonate and the symptomatic measures of caffeine and adrenalin on arrival, blood transfusions, intravenous glucose and saline, 5% glucose and solid sodium bicarbonate by mouth, 5% glucose and 5% sodium bicarbonate (75 cc. of a mixture of equal parts) by rectum, digitalis, colonic irrigations, and "force fluids by mouth" whenever such was possible. The 2 cases of Olmsted and Aldrich[46] reacted favorably to intensive alkali treatment, and were also given a glucose hypodermoclysis with $7\frac{1}{2}$ units of insulin. Solid sodium bicarbonate was mixed with orange juice and given by mouth and in this way 5 gm. of the salt were administered to the child in an hour or two.

In the maintenance of renal function lies the best hope of recovery. As has been shown by Morris and Graham,[45] large doses of alkali more than double the rate of excretion and cause over 90% of the salicyl to be recoverable in the urine. Likewise, they found that in patients given 6 gm. of sodium salicylate and 12 gm. of sodium bicarbonate a day there was no drop in blood CO_2 combining power, no decreased urine output, no abnormal retention of blood constituents, and no evidence of any renal damage. Without the bicarbonate protection there was a decrease of alkali reserve and urine output,

an increase in the blood non-protein nitrogen, and evidences of renal damage in the urine. Johnson[32] shows that twice the amount of sodium bicarbonate is necessary to replace the amount of CO_2 lost from the bicarbonate reserve with a given amount of sodium salicylate. Since methyl salicylate is excreted much more slowly and incompletely and withal is definitely more toxic, three or four times as much bicarbonate are indicated. If a poisoning case is seen within 20 to 25 hours a 6% sodium bicarbonate gavage, with several grams of the salt left in the stomach, is a doubly good measure as it not only allows a large intake of the substance but neutralizes the salicylic acid liberated in the stomach. It is likewise obvious that fluids should be forced in every possible manner as long as no contraindications are manifested. Oral and intravenous glucose solution, usually 5% in strength, has contributed some beneficial effect in the cases where it has been used. Its use is supported experimentally by some work of Madisson[37] who found, in experiments on dogs which had been given toxic doses of sodium salicylate, that oral and intravenous glucose lessened the degree of the usual impairment of renal function and the subsequent pathologic lesions he claims to find in the kidneys.

In cases of poisoning where there is acetonuria, hyperglycemia, and marked acidosis, intravenous glucose with a very small dose of insulin is indicated, as this measure seems to have an advantageous effect upon that part of the acidosis which is due to impaired carbohydrate and fat metabolism.

Blood transfusion is a good general measure in severe cases and was used with evident success in Case 1.

Enemata and high colonic irrigations are indicated because they will help to evacuate the bowel of what methyl salicylate there may be in the feces, will promote good intestinal elimination, and will clean out the colon so that rectal glucose and bicarbonate solutions may be more readily absorbed.

Also, since anuria was described in 1 or 2 cases in which a full urinary bladder was found at autopsy, catheterization should not be refrained from if there is any possible evidence of retention.

In cases where there is a substantially weak pulse, caffeine and adrenalin may be given to advantage, the former for its cardiac stimulation and the latter for its vasoconstrictor power. If there is a continued weak pulse and feeble heart sounds, digitalis is indicated and has been used to definite advantage. Atropine has proved helpful in relieving respiratory distress.

When the alkali reserve is greatly depleted, intravenous sodium bicarbonate, of a 4% or 5% solution, may be given, but it allows the intake of a relatively small amount of the salt and the actual amount to be given must be carefully considered due to its immediate specific reactivity in the blood. About 13 cc. per kilogram of body weight will raise the CO_2 combining power 15 vol. %. It is safer to

give intravenously a ½ molar solution of sodium lactate, and 60 cc. per kilo will raise the CO_2 combining power about 30 vol. %. Excellent results have been obtained from the use of this salt in treating acidosis at the Harriet Lane Home. There is no reason to believe that this salt would have any deleterious effect upon the metabolism or excretion of the slightly increased lactic acid which has been found in the blood in salicylate poisoning.

As far as combating the general systemic effects of the salicyl ion is concerned, three things may be done: To remove the source of supply of the poison—gavage, emesis, and enemata; to promote its excretion—give fluids, sodium bicarbonate and glucose; to replenish the alkali reserve—give the above mentioned sodium salts.

Since the mortality in this type of poisoning is 59%, and that of bichloride of mercury poisoning is 25 to 50%,[30] it seems reasonable that steps should be taken toward its prevention; 41% of the methyl salicylate poisonings occurred accidentally in children under 5 years of age. Thus, if bottles of oil of wintergreen were labelled "Poisonous if taken internally," it would serve to remind parents to keep them under lock and key.

Summary. 1. Three new cases of oil of wintergreen poisoning are reported, and 20 cases hitherto not included in the lists of reported cases were found in the literature. These, with the other known cases, a total of 46, have been summarized. Thirteen autopsy reports were found in the literature, and these, with that of 1 of the author's cases, are summarized. The mortality is found to be 59%, while 41% of the poisonings occurred in infants.

2. The typical case clinically was found to have early vomiting, rapid and deep respirations, rapid pulse, cyanosis, flushed skin and extreme thirst. Then, in the fatal cases, followed stupor, coma, impaired vision and hearing, convulsions, and exodus in respiratory failure. The blood studies showed an average CO_2 combining power of 32.7 vols. %, a non-protein nitrogen of 70.2 mg. %, and a sugar of 152 mg. %. The urine showed a 4+ acetonuria and a positive test for salicylate in all those tested; 60% of the tests for albuminuria were positive. Many urines showed red blood cells and casts.

3. There are no remarkable anatomic pathologic changes, and those which are found are not typical or specific in any way. The chemical changes in the blood and the known pharmacologic properties of the drug indicate that the pathologic physiologic changes are more striking than the anatomic ones. The renal function impairment and the lowered alkali reserve in the blood ("acidosis"), the central nervous system depression, and the interference with the carbohydrate, fat, and nitrogen metabolism are the most important changes.

4. The literature on the pharmacology of methyl salicylate is reviewed with the purpose of correlating the findings and applying them therapeutically. The "acidosis" is found to be mostly a com-

pensated fixed acid acidosis, and is due to retention, by damaged kidneys, of urea and non-protein nitrogen, to an increase in blood amino acids, in blood lactic acid, and to a ketonemia. These last two abnormalities are apparently the result of impaired carbohydrate and fat metabolism; they are also due, to some extent, to protracted vomiting when it occurs.

5. There is conclusive evidence to the effect that the ingestion of 2 to 4 times as much sodium bicarbonate as methyl salicylate helps to prevent the toxic action of the latter and to speed up its excretion and make it more complete. Also, glucose, probably through its diuretic property, has a definite protective effect upon the kidneys in salicylate poisoning.

Aside from an initial thorough gastric lavage, the treatment is symptomatic. One of the chief aims is to protect the kidneys, for in the maintenance of their function lies the chief hope of recovery. This can be done through the ample administration of fluids; calcium lactate and glucose solutions should be given intravenously. Immediate sodium bicarbonate gavage, enemata, and proctoclyses are imperative, and this salt should be administered by mouth in ample amounts. Atropine, caffeine, adrenalin, blood transfusions, and in some cases digitalis are of benefit. If hyperglycemia is discovered, a small dose of insulin given simultaneously with intravenous glucose is beneficial.

6. Since 4 cc. of oil of wintergreen has been lethal in an infant and 6 cc. lethal in an adult, and in view of the high mortality of 59%, it has been suggested that the drug be labelled "Poisonous if used internally."

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THE CLINICAL SIGNIFICANCE OF SERUM PROTEINS IN HEPATIC DISEASES.

Compared with Other Liver Function Tests.

By Henry Tumen, M.D.,

Assistant Professor of Medicine, Graduate School of Medicine, University of Pennsylvania,

and

H. L. Bockus, M.D.,

Professor of Gastro-enterology, Graduate School of Medicine, University of Pennsylvania, Philadelphia.

(From the Gastro-enterological Clinic, University of Pennsylvania Graduate School of Medicine.)

Many investigators have noted alterations in the concentration of the serum proteins during the course of cirrhosis and other types of hepatic disease.[3,5,13,25] A reduction in the serum albumin has been most frequently recorded; the serum globulin is often

elevated and the albumin-globulin ratio reversed according to many observers.

Kerr, Hurwitz and Whipple[15] noted that hepatic necrosis produced by phosphorus and chloroform was associated with lowering of the level of the blood proteins and that liver injury delayed the regeneration of proteins depleted by plasmapheresis. Sawada[22] and also Henriques and Klausen[9] reported that hepatic damage or ligation of the common duct was followed by a decrease in the albumin and an increase in the globulin. The frequent occurrence of hypoalbuminemia in both clinical and experimental liver injury indicates that the liver is concerned with either the manufacture of albumin or the maintenance of its proper level in the blood. It has been suggested that the protein decrease may be due to nutritional disturbances,[25e] defective protein formation,[25c,g] lack of reserve protein-building material normally stored in the liver,[10,15] loss of albumin into the ascitic fluid[25f] or increased capillary permeability causing escape of protein into the tissues.[14] It is evident that further investigation is necessary in order to explain fully the mechanism of serum-protein changes in hepatic disorders.

During the past 4 years we have had the opportunity to study the serum albumin and globulin levels in 45 patients with various hepatic diseases.* This group was composed of the following:

	No. of cases.
Portal cirrhosis	12
Non-obstructive biliary cirrhosis	2
Obstructive biliary cirrhosis	6
Toxic cirrhosis (Mallory)	2
Banti's syndrome with hepatic involvement	2
Metastatic malignancy of the liver	3
Generalized tuberculosis with hepatic involvement	2
Acute hepatocellular damage of various types	10
Obstructive jaundice	6

Serum Proteins in Portal Cirrhosis. In the group of 12 patients with portal cirrhosis (Table 1), a total of 24 determinations of the serum proteins were made. In every instance the albumin was below our accepted low normal of 4.5 gm. %, being 3.5 or less in all but 1 of the specimens examined. A level of 3.97 gm. was obtained in a man (J. F.) without any clinical manifestations of liver dysfunction in whom a small hob-nail liver was discovered at operation for a duodenal ulcer. Repeated determinations over periods as long as 6 months suggest that, when the patient with portal cirrhosis develops a definite hypoalbuminemia, the chance of a subsequent sustained increase in this protein is slight. There seems rather to be a trend downward in the albumin content of the blood in the advanced cases as the disease process continues. However, symptoms antedated our first examinations for periods

* The determinations were made by a modification of Howe's method, as described by Hawk and Bergeim.[7]

that varied from 4 weeks to 2 years, yet the serum albumin was not lower in those patients who had been ill for longer periods before admission. Hypoalbuminemia was noted before the development of ascites in 3 of these patients.

The increase in serum globulin in portal cirrhosis noted by others was not as constant in this series as the lowering of the albumin level. In our laboratory the normal range of globulin is regarded as between 1.5 and 2.5 gm. %. The globulin was above this level

TABLE 1.—SERUM PROTEIN AND LIVER FUNCTION DETERMINATIONS IN PORTAL CIRRHOSIS.

Patient.	Date.	Total protein.	Albumin.	Globulin.	A/G.	Ascites.	Takata reaction.	Galactose.	Bromsulphalein.	Urobilinogen.	Van den Bergh.
J. F.	1/ 3/35	6.09	3.97	2.12	1.87	Neg.	Neg.	2.40	18%	1/60	0.2
C. DeM.	11/ 6/34	5.30	2.24	3.06	0.73	Pos.	Pos.	3.72	18%	...	1.0
N. C.	11/12/32	6.56	2.57	3.98	0.64						
M. M.	5/ 1/35	5.15	2.94	2.21	1.33	Pos.	Pos.	2.98	70%	1/10	7.5
	5/18	5.68	3.07	2.61	1.17	Pos.	Pos.	..	60%	...	3
	5/29	6.84	2.94	3.90	0.75	Pos.					
E. B.	6/29/34	5.46	2.94	2.52	1.16	Pos.	..	..	50%	1/60	0.2
	10/24	4.90	2.17	2.73	0.79	Pos.	Pos.	1.53	45%	1/40	0.2
	11/13	6.09	2.85	3.24	0.87	Pos.	Pos.	..	8%	1/60	0.2
	12/11	5.00	3.00	2.00	1.50	Pos.	Neg.				
B. H.	12/29/35	6.90	3.50	3.40	1.03	Pos.	..	..	30%	....	4
	1/31/36	7.00	2.20	4.80	0.45	Pos.	Pos.	2.04	60%	...	1.5
	2/19	5.10	1.70	3.50	0.48	Pos.					
M. D.	7/26/35	6.06	3.35	2.71	1.23	Pos.	Pos.				
J. R.	2/12/36	6.34	2.94	3.40	0.86	Neg.					
A. R.	4/11/36	6.09	3.14	2.95	1.06	Pos.	Pos.	1.79	33%	1/30	3
H. F.	8/31/34	9.22	3.33	5.89	0.56	Neg.	Pos.	4.60	8%	1/40	0.45
	12/ 5	5.59	3.39	2.20	1.54	Pos.	Pos.	7.37	..	0	9.0
	12/11	4.96	1.78	3.18	0.55	Pos.	Pos.	..	..	...	12.0
	12/18	4.61	2.58	2.03	1.27	Pos.					
A. K.	3/19/35	5.46	3.23	2.23	1.44	Pos.	Neg.	..	55%	1/40	1.2
	4/ 3	5.09	3.17	1.92	1.65	Pos.	..	1.48	35%	1/80	0.5
	5/11	5.67	3.03	2.64	1.14	Pos.					
S. W.	3/26/35	5.61	3.13	2.48	1.26	Pos.	Neg.	4.30	45%	...	0.9
Range	...	4.61–9.22	1.7–3.97	1.92–5.89	0.45–1.87						

Total protein less than 6.5 in 19
Albumin less than 4.5 in all
Albumin less than 3.6 in 23
Globulin more than 2.5 in 16
Alb./glob. less than 1.0 in 10
Alb./glob. less than 1.5 in 20
} Of 24 determinations.

in 16 of the 24 determinations. Usually the decrease in albumin was greater than the increase in globulin, so that the total protein was below the normal limit of 6.5 gm. % in 19 instances. Indeed every patient showed an hypoproteinemia at some time during the period of observation except Case N. C.

Our findings suggest that the diagnostic value of the reversal of the albumin-globulin ratio has been somewhat overemphasized. In the 24 determinations upon these patients with portal cirrhosis, the ratio was less than 1.5 twenty times, being below 1 in ten of these. The globulin level was more variable than that of the albumin.

The ratio of the two proteins to each other fluctuated a great deal during the course of the disease without any striking change in the serum-albumin content, and without there being any apparent variation in the associated liver disturbance.

TABLE 2.—SERUM PROTEIN AND LIVER FUNCTION DETERMINATIONS IN NON-PORTAL CIRRHOSIS OF VARIOUS TYPES.

Patient.	Date.	Total protein.	Albumin.	Globulin.	A/G.	Ascites.	Takata reaction.	Galactose.	Bromsulphalein.	Urobilinogen.	Van den Bergh.
					Toxic Cirrhosis.						
P.B. . .	7/19/34	6.40	1.39	5.01	0.27	Pos.					
	7/25	2.65	1.35	1.30	1.03	Pos.	Pos.	6.84	23%	1/80	0.9
	8/27	7.66	2.56	5.10	0.50	Pos.	Pos.	5.35	45%	1/80	0.65
	10/9	6.80	2.70	4.10	0.65	Pos.					
	11/19	5.31	2.75	2.56	1.08	Pos.	Pos.	..	45%	1/325	0.7
J. S. . .	11/22/32	8.28	4.06	4.22	0.96	Pos.	..	5.64	75%	1/10	15.0
	1/ 3/33	6.56	2.84	3.72	0.76	Pos.	..	6.43	..	1/40	1.75
	1/20	4.84	2.52	2.32	1.08	Pos.	..	3.13	..	...	1.2
	2/15	6.15	2.37	4.28	0.55	Pos.	..	1.07	..	...	0.5
					Non-obstructive Biliary Cirrhosis.						
L. M. . .	2/ 5/35	7.97	3.99	3.98	1.00	Neg.	Pos.	..	50%	1/140	1.2
	5/7	6.41	3.72	2.69	1.39	Neg.	Pos.	..	25%	1/50	2.4
	4/ 7/36	8.47	4.99	3.48	1.41	Neg.	Pos.	..	50%	1/50	3.2
N. W. .	2/ 4/36	5.00	2.56	2.44	1.04	Neg.	Pos.	2.47	60%	1/10	16.0
	2/18	5.86	3.14	2.72	1.15	Pos.	Pos.	..	..	1/10	18.0
	3/17	5.22	2.56	2.66	0.96	Pos.	Pos.	..	..	...	13.5
					Obstructive Biliary Cirrhosis						
E. O'N. .	1/22/35	5.96	3.09	2.87	1.08	Neg.	Pos.	..	20%	1/60	1.3
	2/26	4.18	1.78	2.40	0.70	Pos.					
S. H. . .	4/13/35	4.69	2.40	2.29	1.04	Neg.	Pos.	..	50%	1/60	9.0
A. P. . .	2/17/36	5.78	2.53	3.25	0.79	Neg.	Neg.	2.89	40%	1/20	8.25
	3/24	8.59	4.88	3.71	1.30	Neg.	Neg.	1.10	6%	1/10	0.8
S. G. . .	1/13/36	5.40	3.30	2.10	1.57	Pos.	Pos.	..	30%	...	5.0
H. M. .	11/ 8/34	5.28	2.55	2.73	0.93	Pos.					
M. S. . .	12/ 6/35	4.40	2.30	2.10	1.09	Neg.	Neg.	..	..	Whole urine	14.4
Range .	...	2.65–8.59	1.35–4.99	2.10–5.10	0.27–1.57						

Total protein less than 6.5 in 16 Albumin less than 4.5 in 21 Albumin less than 3.6 in 18 Globulin more than 2.5 in 16 Alb./glob. less than 1.0 in 10 Alb./glob. less than 1.5 in 22	Of 23 determinations.

Serum Proteins in Other Types of Cirrhosis. (Table 2.) We have included 2 men who suffered with the toxic cirrhosis described by Mallory.[18] One of these (P. B.) entered the hospital because of marked ascites of recent onset, giving a history of painless icterus of 3 weeks' duration, 5 months previously. On admission the serum albumin was 1.39 gm. %. During the succeeding 5 months of his life, the albumin varied between 1.35 and 2.75 gm. %, but the globulin fluctuated markedly. The first 2 protein determinations, 6 days apart, may be cited to illustrate this. The albumin was practically constant but the globulin dropped from 5.01 to 1.3, changing the albumin-globulin ratio from 0.27 to 1.03. This

occurred without any demonstrable clinical change and serves to illustrate the tremendous variations which may occur in serum globulin and in the albumin-globulin ratio within brief periods. The other patient with toxic cirrhosis (J. S.) is also of interest because the first examination, 1 month after the onset of his illness, showed the albumin to be only slightly decreased to 4.06 despite very marked jaundice and a positive galactose test. As the illness continued, however, the albumin dropped considerably and reached the low level of 2.37 gm. % after 3 months.

The 2 patients with biliary cirrhosis of the non-obstructive variety both showed albumin deficiency. In 1 of these (L. M.) it was slight and tended to improve. In the other case (N. W.) the albumin decrease was more marked until the patient's death.

TABLE 3.—SERUM PROTEIN AND LIVER FUNCTION DETERMINATIONS IN BANTI'S SYNDROME.

Patient.		Date.	Total protein.	Albumin.	Globulin.	A/G.	Takata reaction.	Bromsulphalein.	Urobilinogen.	Van den Bergh.
M. L.	...	11/20/34	6.63	3.35	3.28	1.20	Neg.	18%	1/90	
		4/ 6/35	6.47	4.69	1.78	2.63	Neg.	25%	1/80	1.4
		4/ 4/36	5.78	4.38	1.40	3.10	Neg.	20%	1/20	0.9
J. A.	...	9/ 6/32	8.59	5.07	3.52	1.44	...	15%	1/40	0.4
		12/14/35	6.99	4.11	2.89	1.42	Neg.	20%	1/20	1.2
		2/25/36	5.78	2.67	3.11	0.86	Pos.	0	1/20	0.3
		3/30	5.16	3.57	1.59	2.25	Pos.	14%	1/30	0.7
		4/21	6.72	3.61	3.11	1.16	Pos.	12%	1/20	0.7
	Serum Protein and Liver Function Determinations in Generalized Tuberculosis With Hepatic Involvement.									
M. B.	...	2/16/35	7.53	3.02	4.51	0.67	Pos.	9%	1/60	Less than 0.2
		4/13	7.65	3.42	4.23	0.80	Pos.	6%	1/100	Less than 0.2
J. L.	...	1/29/35	5.46	2.90	2.56	1.13	Neg.	18%	1/100	0.5
	Serum Protein and Liver Function Determinations in Metastatic Malignancy of Liver.									
	Location, original neoplasm.									
M. C.	Cervix	2/14/35	6.33	3.68	2.65	1.39	Neg.	40%	1/150	2.4
C. H.	Stomach	1/ 7/35	5.75	2.87	2.85	1.00	Pos.	28%	1/40	0.4
H. L.	Stomach	1/29/36	7.50	3.97	3.53	1.12	Neg.	20%	1/40	0.6
		3/30	5.15	3.52	1.63	2.15	Pos.	24%	1/20	1.2

All 6 cases with biliary cirrhosis developing secondary to long-standing common-duct obstruction showed marked albumin deficiency. In 1 of these a low-albumin level on admission returned to normal after 5 weeks, coinciding with improvement in the clinical status and in other liver function tests. In another patient (E. O'N) the initial albumin level was 3.09 gm. %. During the following month she suffered a number of hemorrhages and, although she received many transfusions, when the blood was reëxamined 1 month later it was found that the albumin had decreased to 1.78 gm. %. It is possible that this is a clinical counterpart of the experimental findings of Kerr, Hurwitz and Whipple[5] who found that animals with damaged livers were unable to restore protein lost by bleeding.

Serum Proteins in Other Types of Chronic Diffuse Liver Disease. (Table 3.) The serum-protein behavior in 2 cases having the so-called Banti's syndrome is of interest. One (J. A.) was seen originally in September, 1932, with marked ascites and moderate splenomegaly. The bromsulphalein test was positive, although the serum albumin was normal. He was lost to us until December, 1935, when he appeared with persistent ascites, dye retention and now an hypoalbuminemia. Since splenectomy in January, 1936, progressive liver change is suggested by further decrease in serum albumin and persistence of evidence of liver dysfunction.

This case can be compared with M. L. whose splenectomy was performed in March, 1933, before signs of liver dysfunction appeared. Twenty months later the bromsulphalein test first became positive and the albumin level dropped to 3.28 gm. %. Subsequent examinations at 5 months and 1 year showed persistent retention of bromsulphalein but normal serum proteins. A study of these cases suggests that the liver's function of removing dye from the blood stream is impaired first and is more permanent in Banti's syndrome than is an alteration in the serum proteins. It seems probable that alteration in the serum proteins does not occur in Banti's syndrome until hepatic changes become advanced.

We have included serum-protein studies in 2 patients with generalized tuberculosis who at autopsy showed extensive involvement of the liver. The hepatic damage had been suggested during life by the abnormal response to the function tests used. In both of these cases the albumin was decreased and 1 there was marked elevation of the globulin. To ascribe these changes entirely to the liver injury would probably be unjustified, since in both there were definite nutritional deficiencies. The albumin decrease, however, is similar to that found in other types of hepatic disease.

Three patients with metastatic malignancy of the liver also showed a lowering of the blood albumin. Malnutrition may have been somewhat responsible in 2 cases with a primary neoplasm in the stomach. In both of these, however, a widespread destruction of the liver was found at necropsy.

Serum Proteins in Acute Hepatocellular Damage. (Table 4.) Alterations in the serum proteins are not confined to the chronic hepatic disorders.[25g,i] Determinations were recorded in 3 cases of toxic hepatitis, 6 of so-called catarrhal jaundice and 1 of cholangitis. A fatal case of cinchophen hepatitis and a case of subsiding arsenical jaundice showed hypoalbuminemia. The protein behavior in a man who died of chloroform poisoning was unusual. The first albumin level, 4 days after the onset, was 2.85 gm. % which rose to the normal level of 4.56 just before death 2 days later. The globulin readings were low and the albumin-globulin ratio normal.

Six patients with so-called catarrhal jaundice are included. The albumin was reduced in 5 and the globulin elevated in 4 patients.

In 1 of the patients (S. S.) the albumin returned almost to normal after 2 days as the jaundice decreased and the clinical course improved. The remaining patient in this group of acute disturbances was a man with cholangitis and multiple liver abscesses, in whom nutritional factors may have been at least partly responsible for the low albumin without appreciable increase in the globulin.

TABLE 4.—SERUM PROTEIN AND LIVER FUNCTION DETERMINATIONS IN ACUTE HEPATOCELLULAR DAMAGE.

Patient.	Diagnosis.	Date.	Duration.	Total protein.	Albumin.	Globulin.	A/G.	Takata reaction.	Galactose.	Bromsulphalein.	Urolilinogen.	Van den Bergh.
N. K.	Cinchophen hepatitis	5/ 4/35	2 wks.	5.16	2.76	2.40	1.15	Pos.				
H. S.	Chloroform poisoning	2/20/33	4 days	4.27	2.85	1.42	2.00	..	..	..	1/30	20
		2/22/33	6 days	5.66	4.56	1.10	4.14	..	..	90%	..	30
E. E.	Subsiding arsenical hepatitis	2/13/35	2 mos.	7.25	3.74	3.51	1.06	Neg.	..	6%	1/80	0.7
B. S.	"Catarrhal jaundice," lues	6/ 2/34	20 days	5.22	2.50	2.72	0.91	Pos.	5.6	..	1/10	4.0
S. S.	"Catarrhal jaundice"	9/10/34	12 days	5.25	2.16	3.09	0.69	Neg.	1.5	..	1/100	10.0
		9/12/34	14 days	6.31	4.16	2.14	1.94	..	1.92	..	..	7.5
T. W.	"Catarrhal jaundice," lues, alcoholism	11/25/35	10 days	7.65	4.49	3.16	1.42	Neg.	4.44	30%	1/40	6.0
		12/ 2/35	17 days	10.03	5.52	4.51	1.22	..	....	..	1/80	1.2
B. M.	"Catarrhal jaundice," lues	12/19/35	2 wks.	7.66	4.30	3.36	1.28	Neg.	6.49	20%	..	1.5
W. M.	"Catarrhal jaundice"	7/22/35	7 days	5.20	3.00	2.20	1.36					
E. P.	"Catarrhal jaundice"	1/21/36	7 days	5.22	3.14	2.08	1.51	Pos.	2.453	..	1/100	3.0
J. Q.	Cholangitis, multiple hepatic abscesses	4/28/34	1 mo.	5.31	2.94	2.37	1.24	..	....	7%	..	0.3
Range	....	...	...	4.27–10.03	2.16–5.52	1.10–4.51	0.69–4.14					

Total protein less than 6.0 in 8
Albumin less than 4.5 in 11
Albumin less than 3.6 in 7
Globulin more than 2.5 in 6
Alb./glob. less than 1.0 in 2
Alb./glob. less than 1.5 in 9
} Of 13 determinations.

In these cases of acute hepatocellular damage the globulin levels were lower, and the albumin-globulin ratio less altered than in the cirrhoses. The tendency toward lowering of the albumin level seemed to be greater in those whose illness was more severe. Improvement in the serum-albumin level was not invariably a favorable prognostic sign.

Serum Protein in Obstructive Jaundice. (Table 5.) In 2 cases with carcinoma of the head of the pancreas the albumin was quite low. This may have been due in some measure to the malnutrition of malignant disease as suggested by Peters and Eisenman.[25e] Three

of 4 patients with common-duct stone obstruction of 10 days', 3 weeks' and 3 months' duration, had moderate lowering of the albumin. The levels of the albumin were not decreased in relation to the duration of the jaundice. In the fourth case of incomplete obstruction of 3 months' duration, the albumin reading was practically normal. Our findings in obstructive jaundice suggest that the protein changes are dependent more upon the completeness of the obstruction than upon the duration of the icterus.

Discussion. Analysis of these clinical data does not justify definite conclusions concerning the mechanism of the alteration in the serum proteins in advanced liver disease. The changes were not

TABLE 5.—SERUM PROTEIN AND LIVER FUNCTION DETERMINATIONS IN OBSTRUCTIVE JAUNDICE.

Name.	Diagnosis.	Date.	Duration.	Total protein.	Albumin.	Globulin.	A/G.	Takata reaction.	Galactose.	Bromsulphalein.	Urobilinogen.	Van den Bergh.
M. L.	Carcinoma, head of pancreas	1/13/35	6 mos.	4.156	2.09	2.07	1.01	Neg.	...	..	0	14
G. G.	Carcinoma, head of pancreas	10/18/34	3 mos.	4.00	1.80	2.20	0.81	..	0.17	98%	Whole urine	2.6
W. W.	Common duct stone	4/16/35	10 days	6.15	3.33	2.82	1.18	Neg.	2.60	35%	Whole urine	6.0
E. G.	Common duct stone	1/ 7/36	3 wks.	6.72	3.72	3.00	1.24	Neg.	...	..	...	2.0
S. T.	Common duct stone	11/19/35	3 mos.	5.34	3.88	1.46	2.65	Neg.	...	..	0	2.4
J. L.	Common duct stone	1/ 9/36	3 mos.	6.93	4.46	2.47	1.80	Neg.	0.818	18%	Whole urine	0.7
Range	....	...	...	4.00–6.93	1.80–4.46	1.46–3.00	0.81–2.65					

Total protein less than 6.0 in 3
Albumin less than 4.0 in 5
Globulin more than 2.5 in 2
Alb./glob. less than 1.0 in 1
Alb./glob. less than 1.5 in 4
} Of 6 determinations.

due in most instances to an inadequate protein intake. However, we cannot affirm or deny the rôle of faulty absorption of proteins from the alimentary canal. The strongest argument against this factor is the rapidity with which serum-protein changes occur in acute diffuse types of liver disease. Increased metabolism played no part in the serum-protein changes in these cases. A study of our material justifies the statement that protein loss *via* ascitic fluid is not an important initial cause of hypoalbuminemia. Indeed, it seemed more likely that the reduction in serum albumin may have been responsible to some extent for the abdominal fluid. Hypoalbuminemia was often present in chronic liver disease in the absence of ascites. In most of the acute cases the alteration in blood protein was not associated with peritoneal fluid. It was

often impossible to maintain a normal protein level in chronic cases in spite of an adequate protein supply in the form of blood transfusions or plasma infusions (as suggested by Strumia and Monaghan). Protein loss into the ascitic fluid could not be held responsible in some instances. Therapy was successful in maintaining an adequate protein level only in those cases in which liver function improved as measured by other liver-function tests. The evidence at hand both clinical and experimental favors some fault in liver function *per se* to account for the alteration in blood proteins in hepatic disease. Whether this defect is due to inability to manufacture or synthesize the protein or to ineffectual mobilization remains to be determined.

Serum-protein Levels Compared With Various Liver-function Tests.—This type of comparison was attempted by Mea,[25h] who concluded that a definite parallel existed between albumin decrease and hepatic insufficiency and also by Lupu and Papazian,[16] who

TABLE 6.—COMPARISON OF THE SERUM ALBUMIN LEVEL AND THE RESULTS OF LIVER FUNCTION TESTS.

		Acute Liver Disease. Albumin.			*Cirrhosis of Various Types.* Albumin.	
		Decreased.	Normal.		Decreased.	Normal.
Galactose	Pos.	2	2	Pos.	10	0
	Neg.	1	0	Neg.	3	0
Urobilinogen	Pos.	4	1	Pos.	10	0
	Neg.	1	0	Neg.	4	0
Bromsulphalein*	Pos.	2	3	Pos.	17	0
	Neg.	0	0	Neg.	0	0

* Including both jaundiced and non-jaundiced cases.

reported that changes in protein metabolism were definitely related to variations in the liver function as measured by carbohydrate tolerance. We will first present a consideration of the albumin levels in relation to the results of the galactose tolerance, bromsulphalein and urine urobilinogen tests in patients with cirrhosis and acute hepatocellular damage. The results of the various tests which have been tabulated correspond to the time of making the serum-protein determinations.

Galactose Tolerance Test. Of 13 patients with cirrhosis and hypoalbuminemia who had 1 or more galactose tolerance tests performed (Tables 1, 2 and 6), 10 had a positive response, if an excretion of 2 gm. or more of the sugar after taking a 40-gm. dose is regarded as positive.[1,26] In 3 cases of cirrhosis (all portal) the galactose test was negative, although the albumin was decreased quite as low as in those with positive galactose tests. In the patient (A. P.) with obstructive biliary cirrhosis clinical improvement was associated with a rise in albumin and a return of the previously positive galactose test to normal. However, J. S., with a toxic cirrhosis, showed a steady decrease in albumin during the period that the galactose response became normal.

In 4 of 5 patients with acute liver damage the galactose response was positive (Tables 4 and 6). The serum-albumin was essentially normal in 2 of these and definitely below normal in the remaining 2 cases. The fifth case with a normal galactose tolerance had only a mild catarrhal jaundice (S. S.). His albumin was at first quite low but returned to slightly below normal 2 days later. This comparison suggests that the serum albumin is a less delicate index of acute hepatic damage than the galactose test, but that the albumin determination is the more accurate of the two procedures in indicating the presence of a chronic hepatic disorder. The negative results of the galactose test in chronic liver disease are readily explained by the regeneration in many instances of some functioning tissue, which is apparently inadequate to carry on the protein function.

Urobilinogen Test. Simultaneous urine urobilinogen tests and serum-protein determinations were performed in 14 patients with hypoalbuminemia in the cirrhotic group (Tables 1 and 6). If one considers that a reaction to Ehrlich's aldehyde reagent in urine dilutions of greater than 1 to 20 parts is abnormal, then the test was positive in 10 of these 14 patients. The remaining 4 patients were deeply jaundiced at the time of the examinations.

The urobilinogen test was positive in 5 of the 6 patients with hepatocellular damage upon whom simultaneous protein determinations were available (Tables 4 and 6). In 4 of them albumin was likewise diminished. In the other 1 it was normal. In the 1 instance in which the urobilinogen was normal the albumin was definitely reduced. Excluding cases with jaundice, however, the urobilinogen test was positive in every case in which the serum albumin was reduced both in cirrhosis and in acute hepatocellular damage. In cases with deep jaundice, hypoalbuminemia may frequently suggest definite impairment of liver function, which, of course, cannot be determined by the urobilinogen test as long as bile does not gain access to the bowel or infection arise within the bile channels.

Bromsulphalein Test. It is somewhat more difficult to evaluate the bromsulphalein test in terms of liver dysfunction in the presence of jaundice, which may be obstructive in type. The test was performed in 17 patients with cirrhosis and hypoalbuminemia (Tables 1, 2 and 6). In 7 cases the positive response to the dye test was apparently not dependent on jaundice. The 10 other patients, who were tested with bromsulphalein, were jaundiced and, of course, none excreted the dye normally. Even if one ignores the influence that icterus may have on dye retention and considers that all of these positive bromsulphalein reactions were due to the liver damage, the level of the serum albumin would seem to be at least as accurate a measure of hepatic dysfunction as the bromsulphalein test, since a low albumin was found in each patient who had dye

retention. However, the dye test occupies a somewhat superior place in the diagnosis of cirrhosis without jaundice, since extrahepatic disorders will occasionally cause hypoalbuminemia whereas marked bromsulphalein retention in the absence of icterus is practically pathognomonic of intrahepatic disease.

The bromsulphalein and serum protein determinations were used in 5 patients with acute liver-cell diseases (Tables 4 and 6). The comparison is only of value in 2 of them without clinical icterus. Both showed dye retention and hypoalbuminemia.

Takata Test. Since Jezler's first use, in 1930, of the Takata reaction in the diagnosis of cirrhosis,[12a] numerous contributions on the subject have appeared.[4,8,11,12b,17,20,21,24,27] The consensus of opinion has been that the test is positive in the majority of patients with cirrhosis and that it may be positive in other types of advanced liver disease, including severe acute hepatocellular damage. The

TABLE 7.—THE RESULTS OF THE TAKATA REACTION IN RELATION TO THE SERUM PROTEIN LEVEL. (54 DETERMINATIONS IN 37 PATIENTS.)

Takata Positive (32 Tests).		*Takata Negative* (22 Tests).	
Albumin	Average, 2.97 Range, 1.35–4.99 Less than 3.6 in 28 More than 3.6 in 4	Albumin	Average, 3.54 Range, 2.09–4.88 Less than 3.6 in 10 More than 3.6 in 12
Globulin	Average, 2.96 Range, 1.30–5.89 Less than 2.5 in 10 More than 2.5 in 22	Globulin	Average, 2.70 Range, 1.46–3.53 Less than 2.5 in 9 More than 2.5 in 13
Alb./glob.	Average, 1.09 Range, 0.45–2.25 Less than 1.0 in 11 1.0–1.5 in 16 More than 1.5 in 5	Alb./glob.	Average, 1.38 Range, 0.69–2.65 Less than 1.0 in 2 1.0–1.5 in 16 More than 1.5 in 4

nature of the reaction remains in doubt. Jezler felt that the results varied with the globulin content of the serum, becoming positive when this protein became relatively excessive. This seemed incompatible with the negative findings in such diseases as nephrosis. Other investigators have concluded that while there is usually some lowering of the albumin and elevation of the globulin in the positive reacting sera, that these are not constant findings.[8,17,24] Other theories, advanced to explain the reaction, include the supposed presence in the blood of certain fatty acids,[23] the accumulation of ammonia because of liver dysfunction,[19] and increase in some of the individual globulin fractions.[2,6,11]

It is not our purpose at this time to present in detail our experience with the Takata reaction as a diagnostic measure. The tables show that the Takata reaction was positive in a high percentage of cases with severe chronic liver disease, that it was not specific for cirrhosis of any kind, that it was positive in some cases of acute hepatocellular damage, but that it may be negative even in the presence of advanced hepatic dysfunction.

In reviewing the serum-protein levels determined at the time of performing the Takata reaction, we found that the test was

positive more frequently when the albumin was decreased and the globulin slightly elevated (Table 7). The albumin-globulin ratios were at a somewhat lower level in the positive Takata group. However, when individual cases were studied there was considerable variation noted in the amounts of albumin and globulin in both the positive and negative reacting sera. Thus, the albumin was found to be less than 3.6 gm. % in 28 of the 32 positive sera but it was also below this level in 10 of the 22 that were negative. The globulin was more than 2.5 gm. % in 22 of those reacting positively but it was also above this amount in 13 of those that were negative. However, there were only 5 cases with a positive Takata reaction who showed a normal albumin-globulin ratio, and in these cases the total protein level was reduced. We are, therefore, forced to conclude that although the serum proteins were abnormal in some respect, in practically every case showing a positive Takata reaction, the mechanism is not entirely dependent upon the ratio of the albumin to the total globulin. It is possible that changes in the concentration of the various globulin fractions may be a responsible factor.

Summary. 1. Serum-protein determinations have been carried out on 45 patients with various types of acute and chronic hepatic disease. Hypoalbuminemia was the most consistent alteration noted, being present at some time in every case of chronic advanced liver disease and in most cases of obstructive jaundice. Elevation in the serum globulin and lowering of the albumin-globulin ratio, although usually present, was not as significant or constant as the reduction in serum albumin.

2. Identical serum-protein changes were noted in some cases of acute hepatocellular damage but not with the same frequency or degree as in the cirrhoses.

3. As to the mechanism responsible for the protein changes, our data tend to support the existence of some basic disturbance of liver function to account for the hypoalbuminemia in liver disease.

4. Simultaneous tests of liver function including the galactose, urobilinogen, bromsulphalein and Takata tests were carried out. Their clinical and prognostic values are compared. Further evidence is presented to refute the importance of an inversion of the albumin-globulin ratio *per se* as the mechanism responsible for the positive Takata reaction.

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FURTHER EXPERIENCE IN THE DIAGNOSIS OF HYPERPARATHYROIDISM, INCLUDING A DISCUSSION OF CASES WITH A MINIMAL DEGREE OF HYPERPARATHYROIDISM.

By Fuller Albright, M.D.,

ASSISTANT PHYSICIAN, MASSACHUSETTS GENERAL HOSPITAL; ASSOCIATE IN MEDICINE, HARVARD MEDICAL SCHOOL,

Hirsh W. Sulkowitch, M.D.,

RESEARCH FELLOW IN MEDICINE AND UROLOGY, MASSACHUSETTS GENERAL HOSPITAL,

AND

Esther Bloomberg, B.S.,

RESEARCH TECHNICIAN, MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS.

(From the Massachusetts General Hospital.)

One of the objects of the present communication is to emphasize, as brought out in 1934,[2] the commonness and polymorphism of hyperparathyroidism by the report of 18 proved cases from this hospital in addition to the 17 previously reported from the same clinic. An attempt will be made, furthermore, to analyze why the disease is so frequent in this particular clinic. In fact, the stimulus to this paper came from a publication by Wilder and Howell[16] who, after pointing out that they had been able to collect only 5 cases at the Mayo Clinic in spite of an early and steady interest in the disease, ended by suggesting that the high incidence in Boston and London was due to some regional factor—possibly lack of ultraviolet radiation in hyperparathyroid belts.

Although it is admitted that lack of ultraviolet radiation predisposes to rickets, that rickets is associated with parathyroid hyperplasia, and that a pre-existing hyperplasia might predispose to

adenoma formation, there are considerations which make it seem unlikely that lack of ultraviolet light has much to do with the incidence of the disease. In the first place, there does not seem to be a predisposition to the disease among the colored race. It is pretty well established that the negro is more susceptible to rickets because the pigment keeps out the ultraviolet light. Of the 35 cases of hyperparathyroidism in our series only 1 was in a negress and she was almost white. Clinics with large numbers of colored patients have not reported large numbers of hyperparathyroid patients. The rickets belt and the hyperparathyroid belt do not coincide. Furthermore, other clinics in Boston have not had an undue number of cases. It, therefore, seems of interest to analyze the 35 cases to ascertain, if possible, why the series is so large.

The first possibility that would occur to one is that more cases are being sent to this clinic because of its known interest and experience with the condition. The first patient with hyperparathyroidism studied in this country was at this hospital just a decade ago, so that after all this clinic had several years start on other clinics. Of the 35 patients in the series, however, 22 were first suspected of having the disease after entry into the hospital; only 13, including the first patient, were sent to the hospital already diagnosed or partly diagnosed. It is apparent, therefore, that the large series is not entirely explainable on the fact that patients are being sent to this clinic. There remain 22 diagnoses to account for.

Hyperparathyroidism Without Clinical Evidence of Bone Disease. The second factor is that many other clinics have not yet fully appreciated that bone disease is not necessarily associated with hyperparathyroidism. The disease was discovered by Mandl[10] and DuBois[8] in patients with a marked degree of bone disease; in most physicians' minds the history of the disease is fresh and hyperparathyroidism is almost synonymous with osteitis fibrosa generalisata. Indeed, many investigators believe that the parathyroid hormone acts directly on bone tissue and from this it would follow that bone changes are a *sine qua non* of hyperparathyroidism.[9,13] In the authors' opinion the hormone does not act directly on bone tissue but rather on the phosphorus and calcium equilibria in body fluids; in the state of hyperparathyroidism these changed equilibria lead to increased losses of calcium and phosphorus in the urine; this situation predisposes to bone disease but does not necessitate it. This point of view involves some theoretical considerations which are beyond the scope of this paper. They were discussed in an unpublished paper presented to the Massachusetts Medical Society (1935) entitled, "Is Hyperparathyroidism Necessarily a Bone Disease?" Regardless of the theoretical points, there is no escaping the important clinical fact that many patients with hyperparathyroidism have no symptoms referable to their skeletons, no evidence of bone disease obtainable by roentgenogram,

no elevation of blood phosphatase, and even no evidence of bone disease obtainable by bone biopsy. The first 3 of these points have been stressed before;[1a,2] the following case history is illustrative of the patient with marked hyperparathyroidism and not even any microscopic bone changes.

Case Abstract. Patient No. 25* (M. G. H., No. 340457). The patient, a single, Finnish chauffeur, of 39, entered the hospital on October 4, 1934, because of attacks of right sided pain. He had noted bloody urine with one attack. A retrograde pyelogram showed a right ureteral stone. Past history was non-contributory. The patient had lost 45 pounds by "diet and exercise" during the past 2 years. Physical examination was essentially normal. The stone was removed on October 6, 1934. As with all patients who have a kidney stone, routine serum calcium and serum inorganic phosphorus determinations were done and found to be 11.3 mg. per 100 cc. and 2.3 mg. per 100 cc. respectively. These figures were checked at 12.2 mg. and 2.6 mg. and again at 13.0 mg. and 3.0 mg. These values left no doubt that this patient had hyperparathyroidism of fairly marked degree. Roentgenogram failed to show increased radiability of the skeleton and the serum phosphatase level was normal (3.7 and 3.0 Bodansky units, normal range being 3 to 5 units). On October 27, 1934, Dr. Oliver Cope performed a sub-total parathyroidectomy, tibial biopsy being taken at the same time. The parathyroids were all enormous, 6.8 gm. of tissue being removed (4 normal glands weigh about 0.11 to 0.13 gm.). Figure 1 shows the parathyroid tissue removed; Figures 2 and 3 show low and high power photomicrographs of the tibial biopsy in this patient. It will be noted that the cortex was very thick and showed no rarefaction. Most important of all, however, was the fact that by high power there were no osteoclasts and no fibrosis seen, just fat cells and inactivity (Cp. Fig. 3 with Fig. 4). This demonstrated that bone was not being destroyed. One might otherwise have thought that repair was keeping pace with destruction.

Of the 35 patients in the series, there were 12 who had no clinical or roentgenographic evidence of bone disease. (In only 8 cases was the skeleton involved and not the urological system; in 15 both systems were involved.) Of the 12 cases with no skeletal disease, all but 3 were picked up at the Massachusetts General Hospital. Of these 3, 2 came from clinics intimately associated with this clinic. From this it is apparent that the community at large is not diagnosing hyperparathyroid patients who do not have bone disease. It is of special interest that to our knowledge no case of proved hyperparathyroidism without evidence of bone disease diagnosed during life has as yet been published from other clinics. Venables[15] published a case in which he emphasized the absence of bony deformities, but roentgenographic studies showed bone disease. Therefore, to carry on the arithmetic, it seems fair to conclude that the 9 cases without bone disease diagnosed at this hospital would not have been picked up at most other clinics. If one subtracts these 9 from the 22 cases diagnosed here, there remain 13 cases unaccounted for. This is still a high number.

* The patients are numbered according to the chronological order in which this disease was demonstrated by surgery. The same numbers are used in all publications from this clinic dealing with the same individuals.[5,6]

Patients with bone disease in whom the bone disease was only found after the diagnosis of hyperparathyroidism was established should really be considered with those without bone disease as far as the present discussion is concerned. There were 7 such cases, all diagnosed at this hospital. Subtracting these 7 from the remaining 13 one is left with 6 cases unaccounted for.

Cases With a Minimal Degree of Hyperparathyroidism. There still remains a third factor to explain the high incidence at this

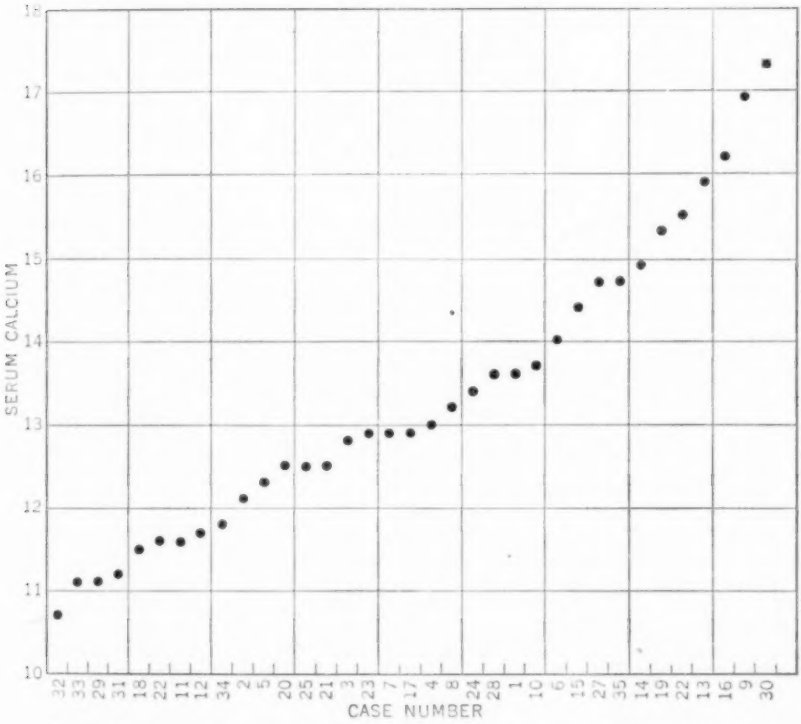

CHART I.—Average pre-operative serum calcium values on first 35 patients at Massachusetts General Hospital with hyperparathyroidism proved by operation.

hospital and that is the diagnosis of patients with a minimal degree of hyperparathyroidism. The nature of the disease is such that it is obvious that there will be cases ranging from a marked degree of hyperparathyroidism all the way down to the normal state. The less the degree of hyperparathyroidism, the less the chemical changes will be from the normal, and the more difficult the diagnosis will be. Shelling[12] gives 12.5 mg. as the lower limit of the serum calcium level in hyperparathyroidism. This figure is too high as is shown by 11 proved cases in this series in each of which the average serum calcium level before operation was below 12.5 mg. (v. Chart I). Most of

these never had values above 12.5 mg.; many others had individual values below 12.5 mg. (v. Chart II). Shelling makes the following statement which requires amplification. "Albright, Aub, and Bauer[2] described a case, interpreted as hyperparathyroidism, in

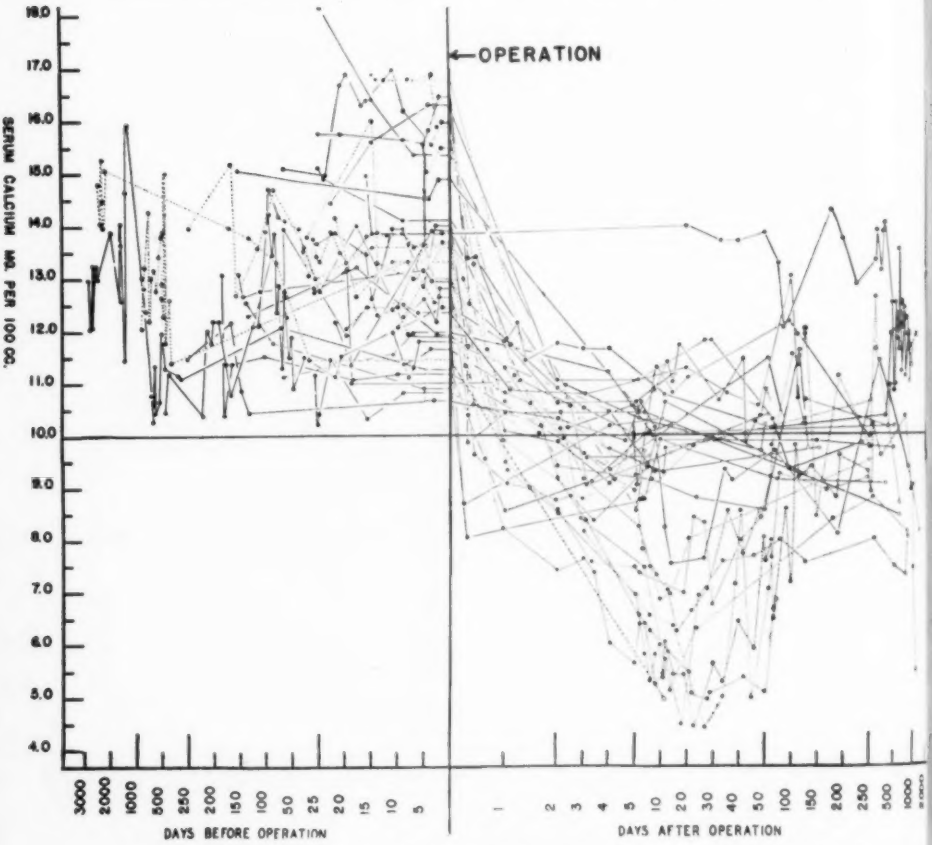

CHART II.—Pre-operative and postoperative serum calcium values on 35 proved cases of hyperparathyroidism from this hospital clinic. Values connected by dotted lines are on patients with high serum phosphatase levels. Final value on each patient is represented by circle instead of dot. Asterisks denote points at which secondary parathyroid operations were done. Note that cases represented by high serum phosphatase levels (and, therefore, having bone disease) are distributed evenly at various levels of hypercalcemia pre-operatively; however, postoperatively these all develop marked hypocalcemia.

which the concentration of calcium in the serum was only 11.5 mg. per cent, but the symptoms consisted only of lassitude, colic, and nephrolithiasis, the roentgenogram of the bones showing no evidence of demineralization, the plasma phosphatase remaining within normal limits, and the palpable tumor of the neck being a thyroid, instead of a parathyroid, adenoma." In this patient, No. 12 in

our series, he neglected to add that a parathyroid tumor was found and removed at operation.

In Chart II the pre- and postoperative serum calcium levels are recorded on all 35 cases. From the pre-operative values it is clear that the serum calcium is evenly distributed from values in the normal range all the way up to very high values. It must be emphasized that whereas this borderline group of patients may have a minimal degree of hyperparathyroidism, they still have sufficient to be disabled or killed. Therefore, the discussion of the diagnosis of this group becomes more than an academic question.

If the serum calcium level itself is not sufficiently high to strongly suggest the disease, one can still be lead to the right diagnosis if the serum phosphorus is persistently low (v. infra; Cases 18, 31, 32), or if the calcium excretion is increased in the urine (v. infra; Cases 32, 33), or if the clinical picture fits the disease and no other disease (v. infra; Case 33). In this group, furthermore, it is important to do repeated determinations as the values fluctuate from the normal range into the definitely hyperparathyroid range (v. infra; Cases 31, 32, 33). If the case is one of nephrolithiasis the fact that the stones contain a large amount of calcium phosphate, and that there are no other obvious causes for stones such as infection or obstruction, become additional points in the diagnosis.

There is one other point, which while quite obvious, is so important that it requires a paragraph to itself. In this group of patients where small changes in the serum calcium level are significant, the serum protein determination becomes of the utmost importance (v. infra; Case 32). It has been shown by McLean and Hastings[11b] that the calcium in the serum is in two states, that in ionized form and that bound to protein. The serum calcium determination measures both together. The amount bound to protein is a function of the amount of protein (as well as of the amount of ionized calcium and pH); the amount of ionized calcium depends on the degree of hyperparathyroidism. Thus the ionized calcium may be slightly high due to a mild degree of hyperparathyroidism, but if at the same time the patient has a low serum protein level, the other fraction will be low, so that the total calcium may end by being normal. It, therefore, becomes necessary to make a correction in the calcium values for low serum protein values. This can easily be done from a linear chart published by McLean and Hastings.[11b]

Case Abstract. Patient 32 (P. H., No. 36569), a married woman aged 48, of Buffalo, N. Y., consulted the clinic on February 21, 1936, because of bilateral kidney stones. Her first symptoms of nephrolithiasis had developed in 1932. A stone had been removed from the right kidney in 1933. She took large amounts of milk. There were no bone symptoms. Physical examination was non-contributory. Roentgenograms showed multiple bilateral renal calculi and normal appearing bones. The urine showed large amounts of calcium and phosphates to rough tests; no albumin; no bacteria (sterile culture); a few red cells and no white cells. The stones in her right kidney which were causing considerable pain were removed by

TABLE 1.—PRE-OPERATIVE AND POSTOPERATIVE DATA ON PATIENT 32.

Date.	Serum per 100 cc. Ca, mg.	P, mg.	Phosphatase, Bod. Units.	Protein, gm.
2/24	11.2	2.8		
2/26	10.2	2.5	3.4	
2/27	10.4	2.1		
2/29	11.5	2.6		
3/7	10.3	2.5	...	4.9
3/14	10.8	2.9	...	5.2
3/23	Parathyroid operation			
3/26	9.6	4.2		
3/31	9.6	3.6		

Dr. George G. Smith on March 4, 1936. In Table 1 the important blood chemical data are recorded. Before operation the serum calcium values with possibly two exceptions were within normal limits; the serum inorganic phosphorus level was persistently low; the serum phosphatase was normal (*cf.* no bone disease). A normal serum calcium value coupled with a low phosphorus value is very suggestive of hyperparathyroidism in a person with a low serum protein. The latter determination was accordingly done and found low. If one corrects the serum calcium values on March 7th and March 14th, when the serum protein values were 4.9 and 5.2 gm. respectively, for what they would have been at a serum protein value of 6.5 gm. one obtains, instead of 10.3 and 10.8 mg., 11.9 and 12.0 mg.* The corrected values were highly suggestive of hyperparathyroidism. In addition, the patient excreted 263 and 222 mg. of calcium per 24-hour period while on a low-calcium diet, normal being about 65 mg. The stones were largely calcium phosphate; there was no other cause for the stones found—no obstruction—no infection. A diagnosis of mild hyperparathyroidism was made. On March 23, 1936, Dr. Edward D. Churchill removed a small adenoma of the left lower parathyroid (1.1 by 0.6 by 0.3 cm.) (v. Fig. 5).

This patient is an excellent example of the importance of the serum protein determination; she illustrates, furthermore, the value of urinary calcium determinations for confirmatory evidence.

Patient 18, Janilly F. (M. G. H., No. 336257, previously published[5]), a married woman, aged 58, was sent to this hospital by Dr. H. Goodale, of

* To obtain the "corrected serum calcium" value one may use the following equation, which was derived from the basic equation of McLean and Hastings[11] for the ionization of calcium proteinate.

$$[\text{Total Ca}] = \frac{[Ca^{++}] \times ([Ca^{++}] + [\text{total prot}] + K)}{K + [Ca^{++}]} \qquad (1)$$

However, before this may be done, the calcium ions in the given serum of lowered serum protein content must be calculated from the following equation of McLean and Hastings:[11]

$$[Ca^{++}] = \frac{[\text{total Ca}] - [\text{total prot}] - K + \sqrt{4K[\text{total Ca}] + ([\text{total prot}] - [\text{total Ca}] + K)^2}}{2} \qquad (2)$$

Ca^{++}, total Ca, and total prot represent millimols per kilo of water and $K = 10^{-2.22}$ in both equations. Water (in gm. per 100 cc.) = 99.0 − 0.75 P (P = gm. of protein per 100 cc.). Total protein in millimols may be obtained by multiplying protein in gm. per liter of water by the Van Slyke, Hastings, Hiller and Sendroy[14] factor $\frac{0.243}{2}$ assuming a pH of 7.35 and an albumin to globulin ratio of 1.8. A correction for the decreased water content (*vide supra*) of the serum with the normal serum protein content will have to be applied to the total Ca of equation (1) to obtain the total Ca in the serum of normal protein content. It is to be noted that the square in the term $([\text{total prot}] - [\text{total Ca}] + K)^2$ was left off in the original article[11a] as a result of a misprint.

Worcester, because the clinical picture appeared to be that of hyperparathyroidism, although the blood chemistry did not seem to confirm the diagnosis. Ten years before admission she had slipped on a wet floor and had fractured her left femur. Ever since then she had had a residual lameness requiring crutches. Nine months before admission she had fainted on a hot day and had again fractured her femur and in addition her left humerus. The hip fracture had not united. There had been no symptoms referable to the urinary tract, but she had lost considerable weight (over 50 lbs.) and strength during the past 10 years. Her diet had not been inadequate. She had lost perceptibly in height. The interesting points on physical examination were adentia, a palpable nodule in the thyroid region (later demonstrated as a thyroid nodule), a moderate hypertension, a thoracic kyphosis, and the changes in her left leg. Roentgenograms showed generalized decalcification, cyst formation, and the ununited fracture of the middle third of the left femur. There was no evidence of kidney disease.

The calcium and phosphorus values before operation were suggestive of a mild hyperparathyroidism. (Table 2.) There were two surprises. It was

TABLE 2.—PRE-OPERATIVE AND POSTOPERATIVE DATA ON PATIENT 18.

	Serum per 100 cc.		
Date (1934)	Ca, mg.	P, mg.	Phosphatase Bod. Units.
4/4	11.4	2.5	
4/10	11.7	2.8	5.7
4/13	Parathyroid operation		
4/17	9.8	3.5	
4/23	9.3	3.3	4.8
4/25	9.7	3.3	
(1935)			
5/16	9.9	2.1	7.5

unusual that a person with so little hyperparathyroidism should develop so much bone disease; furthermore, with the presence of marked bone disease why was the phosphatase level not definitely elevated? The prediction was made that the patient would have a very small tumor and that a bone biopsy would show mostly osteoporosis with relatively little bone destruction and bone formation. The reasoning was as follows. The amount of bone present depends on the balance between bone destruction and bone repair. In senile osteoporosis, the primary trouble is with bone repair. In hyperparathyroidism with bone disease, the primary trouble is increased bone destruction which is partly met by increased bone repair. If the two diseases should coincide, a mild degree of hyperparathyroidism might lead to a small amount of bone absorption, which, if not offset by an equal amount of bone repair because of an associated senile osteoporosis, would result in a marked decrease of bone tissue. In such a situation the serum phosphatase level being an index of the amount of bone repair would not be elevated and would form an exception to the general law that the phosphatase level is an index to the amount of bone disease.

The patient was operated upon by Dr. E. D. Churchill and a parathyroid adenoma 1.2 by 0.8 by 0.4 cm. was removed. A semilunar area of normal parathyroid tissue was present at one end. The tibial biopsy confirmed the pre-operative hypothesis (v. Fig. 6). The patient showed marked improvement during the next year; she gained 25 pounds; roentgenograms showed increased density of bones. The ununited fracture because of bad position remained ununited. The patient refused an open reduction.

Patient 31, Esther S. (M. G. H., No. 346778), a married woman, aged 34, was admitted to the Urological Service in July, 1935, because of pain in the right flank. Bilateral renal calculi were found; two stones were removed from the right ureter and patient was discharged.

TABLE 3.—PRE-OPERATIVE AND POSTOPERATIVE DATA ON PATIENT 31.

Date (1935)	Serum per 100 cc. Ca, mg.	P, mg.	Phosphatase, Bod. Units.
7/15	13.1	2.4	
7/17	Ureterolithotomy		
7/20	10.4	2.7	
7/25	11.4	3.4	3.7
10/10 (1936)	11.5	2.8	
1/1	11.1	2.7	
1/9	....	2.7	4.7
1/13	11.2	2.9	
1/22	Parathyroid operation		
1/27	9.4	4.2	

In Table 3 the pre-operative and postoperative chemical data are shown. The first determination was almost diagnostic of hyperparathyroidism, provided it could be checked. However, it could not be. The serum inorganic phosphorus figures were with one exception consistently low. Unfortunately the serum protein was not determined. The serum phosphatase was normal, which agreed with the fact that there was no bone disease demonstrable by roentgenogram. The calcium excretion in the urine by rough tests seemed increased. The stones were largely composed of calcium phosphate.

On January 23, 1936, Dr. Oliver Cope removed a parathyroid adenoma 1.5 by 1.0 by 0.4 cm., weighing 0.45 gm. This tumor again was so small that a rim of normal parathyroid tissue extended more than half around the tumor (v. Fig. 7). This patient illustrates very well the importance of doing repeated blood determinations. Thus if the first determination had been that of July 25 it is probable that the diagnosis would not have been made until the patient returned to have more stones removed.

Patient 33, Mary McD. (M. G. H., No. 320925), first entered the Urological Service in April, 1932, for a questionable renal tuberculosis and was discharged with the diagnosis of pyelonephritis. She complained at that time of pain in the kidney region and showed pyuria and albuminuria. Urine culture showed a B. coli infection. Roentgenographic studies of the kidneys showed calcium deposits in the region of the pyramids (Fig. 8). This unusual roentgenogram later was brought to the attention of one of us (F. A) and it was realized that calcium deposits in the collecting tubules is very suggestive of hyperparathyroidism with Type II renal lesions.[3] Accordingly, the patient was asked to return for blood chemical studies. It was then noted that her urine contained in addition to the pus many calcium phosphate casts showing that the Type II renal lesions were still being added to.[4]

TABLE 4.—PRE-OPERATIVE AND POSTOPERATIVE DATA ON PATIENT 33.

Date (1935)	Serum per 100 cc. Ca, mg.	P, mg.	Phosphatase, Bod. Units.	Protein, gm.
6/29	11.5	3.1		
7/6	12.2	3.5		
11/5	10.9	3.6		
11/9	....	...	....	6.1
11/19 (1936)	10.5	3.0	11.1	
3/31	10.7	3.7	8.2	
4/2	Parathyroid operation			
4/4	10.2	3.8		
4/7	10.6	3.8		
4/18	11.2	3.8	4.2	

FIG. 1.—Photograph of parathyroid tissue removed at operation on Patient 25. Area enclosed by dotted line adjacent to right lower parathyroid gland represents amount of tissue left in place.

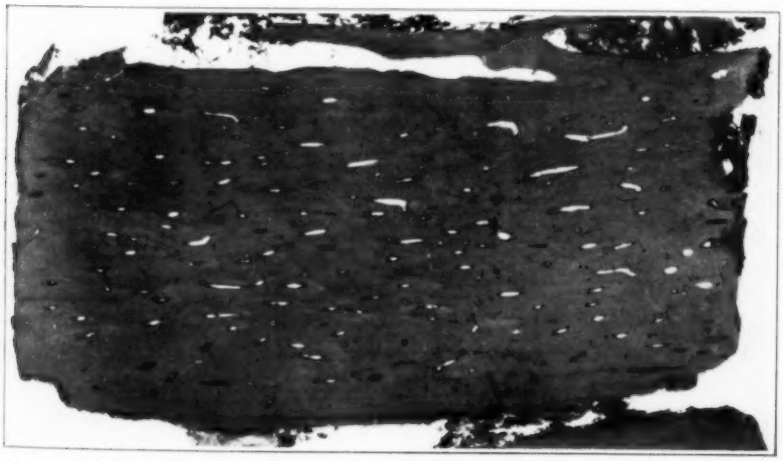

FIG. 2.—Low-power photomicrograph of tibial biopsy on Patient 25 performed at time of parathyroid operation. Note solidity of bone.

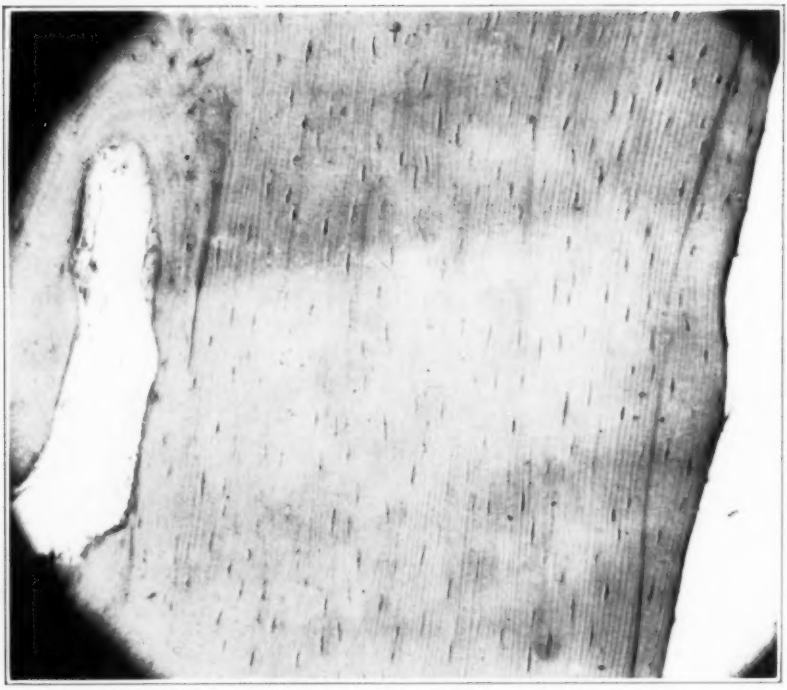

FIG. 3.—High-power photomicrograph of same specimen shown in Fig. 2. Note absence of bone formation, bone destruction, and fibrosis (*cf.* Fig. 4).

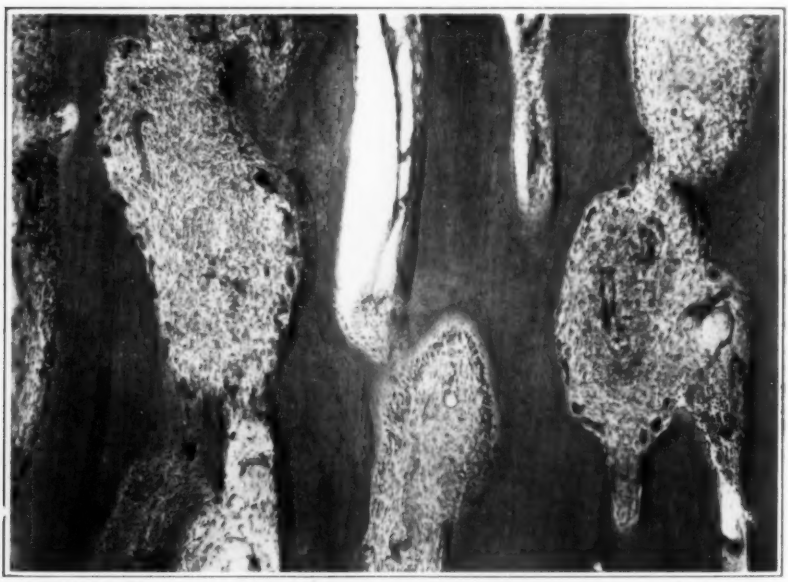

FIG. 4.—High-power photomicrograph of tibial biopsy on patient with hyperparathyroidism and bone disease for comparison with Fig. 3. Note marked bone destruction (osteoclasts +++), marked bone formation (osteoblasts +++), and fibrosis.

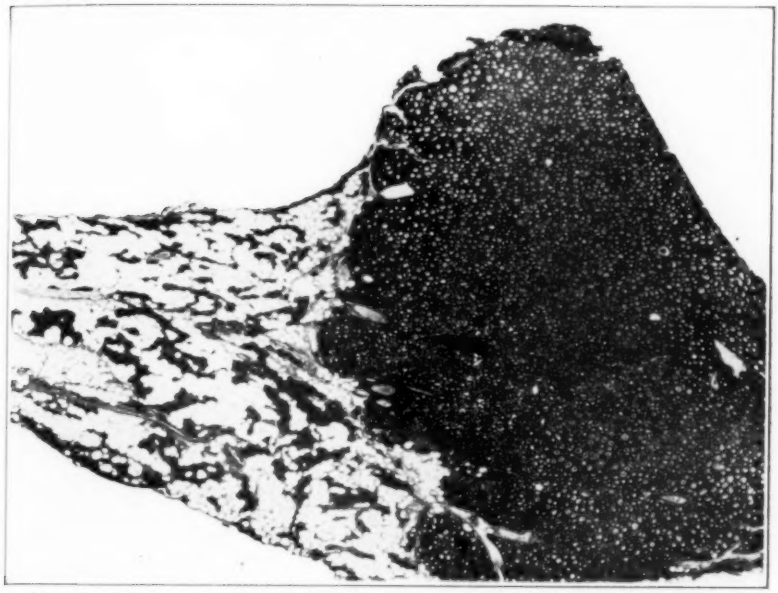

FIG. 5.—Photomicrograph of parathyroid tumor on Patient 32. Note that a large pedicle of normal parathyroid tissue is still intact. Note colloid in tumor, which might suggest thyroid tissue to inexperienced pathologist. Tumor and remainder of gland weighed 0.18 gm. Tumor measured 1.1 by 0.6 by 0.3 cm.; remainder of gland measured 0.7 by 0.3 cm.

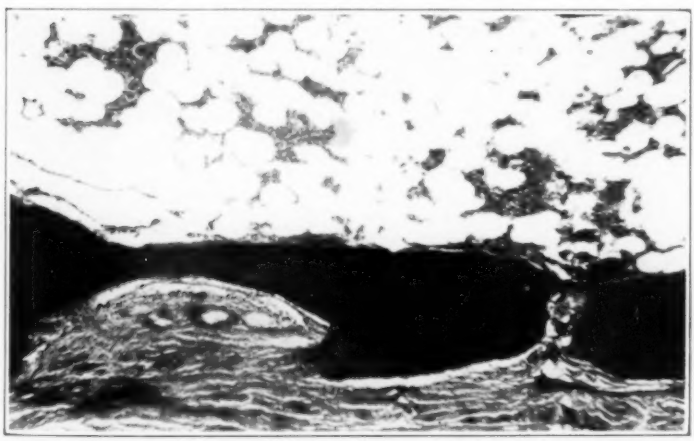

FIG. 6.—Photomicrograph of sternal biopsy on Patient 18. Note absence of any marked evidence of bone destruction or of bone regeneration (*cf.* Fig. 4). See text for discussion.

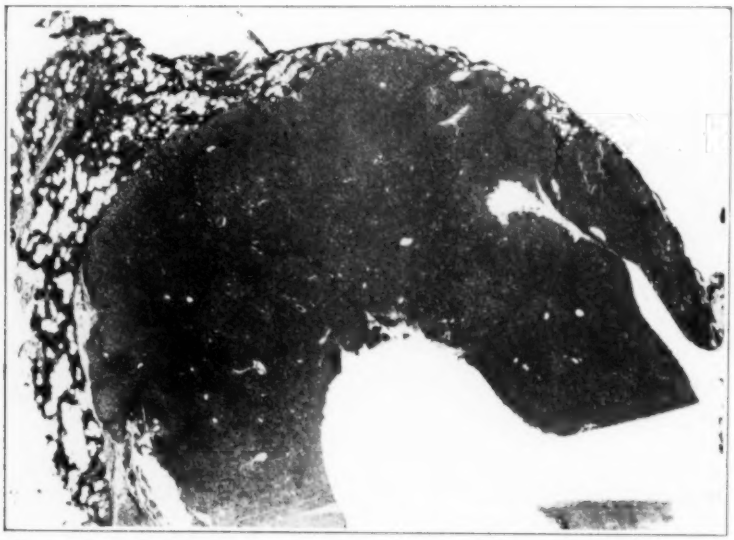

FIG. 7.—Photomicrograph of parathyroid tumor on Patient 31. Note that small tumor is almost completely surrounded by collar of normal parathyroid tissue. Gland and tumor measured 1.5 by 1.0 by 0.4 cm. and weighed 0.45 gm.

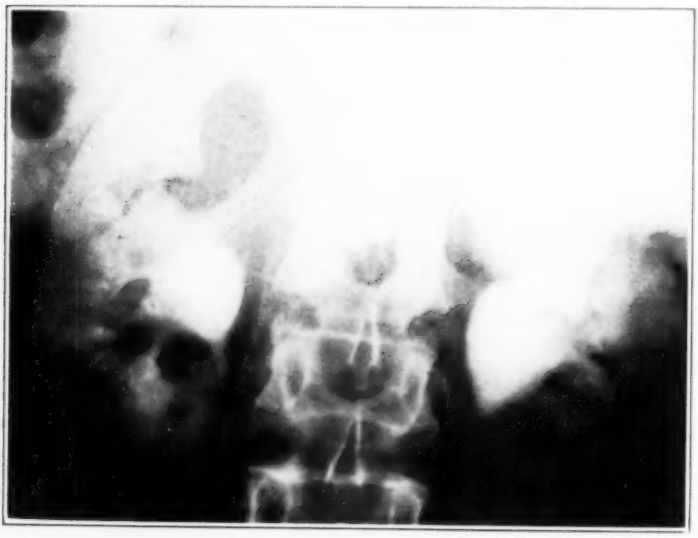

FIG. 8.—Intravenous pyelogram on Patient 33. Note calcium deposits in pyramids of kidneys, a finding very suggestive of hyperparathyroidism.

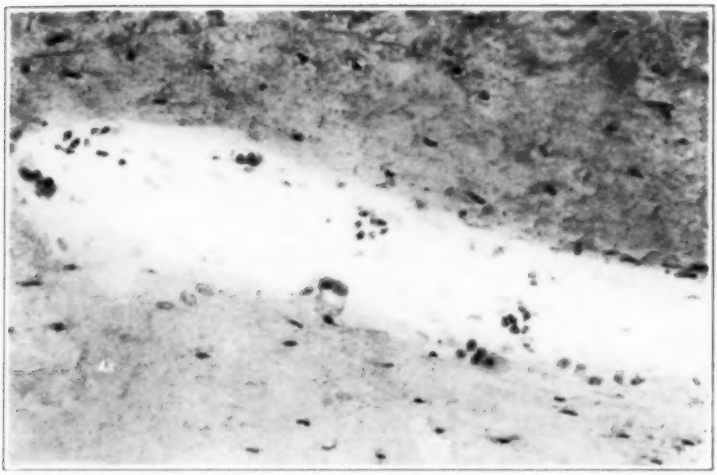

FIG. 9.—Photomicrograph of tibial biopsy taken at time of parathyroid operation on Patient 33. Note nest of osteoclasts, showing that, in spite of mild degree of hyperparathyroidism, bone resorption was occurring.

FIG. 10.—Photomicrograph of parathyroid tumor in lower pole of otherwise normal gland. Tumor was found at autopsy on a patient who had had renal calculi (see text).

In Table 4 her pre-operative and postoperative chemical data are shown. The pre-operative data were certainly not very convincing of hyperparathyroidism, especially the blood taken on March 31, 1936. The phosphatase was slightly elevated and she did show evidence of bone disease by roentgen-ray with generalized decalcification and a wedge-shaped fifth lumbar vertebra. It seemed important to study her calcium and phosphorus excretions. On a neutral-ash low-calcium diet she excreted in her urine per 3-day period 537 mg., 523 mg., and 614 mg. (the average normal value being 190 mg.[7]).

On April 2, 1936, Dr. Oliver Cope removed a parathyroid tumor measuring 0.8 by 0.6 by 0.3 cm., and weighing 0.16 gm. The casts immediately disappeared from her urine.*

This patient was selected for special consideration partly because she had a mild hyperparathyroidism in spite of almost normal blood values, but mostly because she was developing a serious kidney situation in spite of her very mild degree of hyperparathyroidism, as well as definite bone changes (Fig. 9). Why she should develop this type of kidney lesion and another patient should develop stones in the kidney pelves is not known. The diagnosis in this case depended on the clinical picture and the hypercalcinuria.

In the series of 35 cases there were 8, including the 4 cited, which are being classified as borderline cases. In most of these the tumor was so small that it had not entirely destroyed the parathyroid gland in which it was situated. The cases, it is believed, were milder as regards the degree of hyperparathyroidism than any other single proved case yet reported from other clinics, and, therefore, it is argued, they presumably would not have been picked up in most other clinics. All but 2 of these cases fall into previous groups. Subtracting these 2 cases from the 6 there remain only 4 cases unaccounted for.

This is not all. Of the remaining 4 cases, 2 were extremely unusual and cannot be grouped with other cases. One was the girl aged 13 with marked renal insufficiency reported by Albright, Baird, Cope and Bloomberg,[3] a case which remains unique, and in the other patient the diagnosis was arrived at almost by accident and was the subject of a separate communication by Albright.[15]

There remain, therefore, out of 35 cases only 2 which were not sent to this hospital and were not entirely different in character from cases diagnosed elsewhere. A series of 2 cases about corresponds with that of other clinics of similar magnitude. The corollary to the discussion is that if lack of ultraviolet radiation has caused the large series here, there remains to be explained why the type of case also varies so widely from that found elsewhere. Of the 13 cases sent to this hospital on the other hand, 9 were the classical type, 3 were the cases without bone disease discussed above, and the remaining 1 was Case 18, abstracted above.

Additional Discussion. In Chart II some further interesting

* This patient's urinary calcium excretions on a neutral-ash low-calcium diet, per 3-day period, during February, 1937, were: 304 mg., 373 mg., 578 mg. The third of these values is still distinctly high, but the first two were sufficiently within normal limits to rule out hyperparathyroidism.

points are brought out related to the presence or absence of bone disease. As pointed out in a previous paper, a high serum phosphatase level is indicative of marked bone disease, in that this value is proportional to the amount of bone repair. This law of course holds only when bone repair is proportional to the amount of bone destruction present. Thus in Case 18, which is construed as having had a fundamental disturbance in bone repair (*i. e.*, senile osteoporosis) coupled with a mild hyperparathyroidism, there was marked bone disease without an elevation of serum phosphatase. In Chart II, the serum calcium values of patients with high serum phosphatase levels have been connected with broken lines rather than full lines. Two things are apparent. The patients with bone disease (high phosphatase levels) were not necessarily the ones with the severest degree of hyperparathyroidism, but are distributed along at all levels. Following operation this group of patients developed marked hypocalcemia. This chart shows why it has been repeatedly emphasized that patients with high phosphatase levels should be handled very conservatively regarding the removal of parathyroid tissue. In fact, in most cases they should have their tumors resected rather than entirely removed at the first operation.

From the discussion above it is apparent that the diagnosis of hyperparathyroidism has been made with quite slight chemical changes from the normal. It would be misleading not to point out that there have been 3 patients indistinguishable from the borderline cases discussed above in which exploration was performed without the finding of a parathyroid tumor. Such a case was the following.

Patient, Albert H. (M. G. H., No. 352487), a 41-year-old chauffeur, passed his first urinary calculus 18 years before entry and a second stone 2 years before entry. He passed smaller stones subsequently. On March 17, 1936, a stone was removed from the left ureter by Dr. Richard Chute. Chemical analysis of his stone showed it to be largely calcium phosphate. The chemical data on his serum were as follows:

Date.	Calcium, mg.	Phosphorus, mg.	Protein, gm.	Phosphatase:
3/29/35	11.5	2.3		
4/1/35	10.7	2.8		
3/26/36	9.7	2.8	5.4	
4/11/36	10.8	2.8	...	2.9 Bod. U.

The patient was put on a neutral-ash low-calcium diet and excreted in his urine per 3-day period 838 and 839 mg. of calcium (normal being about 190 mg). There was no bone disease demonstrable by Roentgen-ray (*cf.* normal serum phosphatase level).

A parathyroid exploration was performed by Dr. Oliver Cope on April 13, 1936. Three normal appearing parathyroid glands were found; the fourth was not demonstrated; no tumor was found. And yet this patient had a very high urinary calcium excretion, a persistently low serum inorganic phosphorus level, a serum calcium value on the high side (especially when allowance is made for the low serum protein), and the right kind of stones.

The question arises whether these patients with negative explorations represent faulty diagnoses or whether tumors were present and not found. This question cannot be answered. In no one of these particular 3 cases, were all 4 parathyroid glands found. Even if they had been, the possibility exists that the tumor might have been so small that it was mistaken for a normal gland, or was entirely embedded in a normal gland. Such a possibility seems fantastical but the following case brought to our attention by Dr. Benjamin Castleman at least suggests the possibility.

Patient, Alice S. (M. G. H., No. 328221), entered the Urological Service in April, 1933, at the age of 30. She had been in good health until 6½ years before admission when she had begun to pass gravel. A suprapubic cystotomy had been done in 1927 with the removal of stones. A urinary fistula had persisted ever since. She had a badly infected urine and a high nonprotein nitrogen level in the blood. A bilateral nephrostomy was performed, but she died on her 25th postoperative day. No calcium and phosphorus studies were performed.

Autopsy revealed a "bilateral pyohydronephrosis." There was a minute parathyroid adenoma in one of the glands (Fig. 10).

The question is, of course, whether this minute tumor caused hyperparathyroidism, renal calculi, and death. If it did, it is obvious that tumors as small as this could not be recognized with the naked eye and might be entirely surrounded by normal parathyroid tissue. It is an interesting and important question.*

Summary and Conclusions. 1. This paper is based on 35 cases of hyperparathyroidism proved by operation studied at this hospital. It represents a 10-year experience.

2. This series comprises 13 cases sent to the clinic already suspected of having the disease and 22 cases first diagnosed here. All but 2 of the 22 cases had clinical findings entirely different from cases being reported in the literature from outside clinics. The conclusion is made that the series is so large because cases are being recognized which are being missed by other clinics.

3. There are two groups of cases in particular which have accounted for multiple cases at this hospital and which are not being recognized elsewhere. These are:

a, Cases with no demonstrable bone disease—12 cases.

b, Cases with a very moderate degree of hyperparathyroidism—8 cases.

4. The presence or absence of bone disease is not a function of the degree of hyperparathyroidism, some of the severe cases not having

* Dr. Bruce Chown, of The Children's Hospital of Winnipeg, Canada, communicated with Dr. Benjamin Castleman about a somewhat similar case A woman aged 46, who died of rupture of an aneurysm of the circle of Willis, had at autopsy a minute adenoma composed of oxyphil cells in one of the parathyroid glands. She had had a nephrectomy for stone in 1928. The remaining kidney at autopsy was somewhat enlarged and microscopically showed small areas of chronic nephritis and minute calcium deposits. Dr. Chown expects to publish this case in detail, but has kindly consented to our mentioning it.

it, some of the mild ones having it. Patients with bone disease and high serum phosphatase levels as a rule develop postoperative hypocalcemia; other cases seldom do.

5. The term "border-line" has been applied to mild cases of hyperparathyroidism and refers to the degree of hyperparathyroidism, not to the symptoms. In the diagnosis of such cases the following points may be important:

a, The serum protein determination, so that allowance can be made for the "bound" calcium in interpreting the total calcium value.

b, A persistently low serum phosphorus level.

c, The calcium excretion in the urine.

d, The composition of the stone.

e, Repeated blood determinations.

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ADRENAL CORTICAL ADENOMA WITH ABSENCE OF THE OPPOSITE ADRENAL.

Report of a Case With Operation and Autopsy.

By F. D. W. Lukens, M.D.,

Harrison F. Flippin, M.D.,

and

F. M. Thigpen, M.D.,

Philadelphia.

(From the George S. Cox Medical Research Institute and the Medical Clinic of the Hospital of the University of Pennsylvania.)

It is now generally recognized that many or all of the features of Cushing's syndrome may be associated with a variety of endocrine tumors. Basophilic adenomas of the pituitary, adrenal cortical tumors, arrhenoblastomas and thymic carcinomas have all been

described as causes of the clinical picture related to the pituitary by Cushing.[3] The following case displayed almost every feature of Cushing's syndrome and is presented because the problems of diagnosis and treatment can be related to the pathologic findings.

Case Report. The past medical history was not significant.

Present Illness. Began in 1932 at the age of 25 to gain rapidly in weight (20 pounds) and had pain in the legs. Shortly after she noted loss of hair on the scalp, increased appetite, thirst, polyuria and increased huskiness of her voice. The menses, which had begun at 12 years and been normal and regular, became scanty and irregular in 1933, when she also noted purple striations on her abdomen, a bluish discoloration of her feet and excessive growth of hair on her face, back and arms. She also noticed frequent ecchymoses over the dependent portions of her body. Complete amenorrhea developed in April, 1935, at which time she experienced a dull persistent pain over the right lumbar region. She believed that she had become shorter in stature during the past several years.

Physical Examination. She was a somewhat sluggish, young, white woman of plethoric appearance, with marked abdominal obesity, her height being 56 inches and her weight 150 pounds. Her face was very round and full, causing the eyes to appear slightly shut. The obesity was limited to the face, thorax and abdomen (Fig. 1). Over the breasts, axillæ and abdomen there were many prominent purple striations and the lower legs were cyanotic. The skin was dry, coarse and inelastic. Over the cheeks, upper lip, chin and back there was an excessive growth of hair. The hair on the back was perhaps the most strikingly masculine of all these regions. There was partial baldness of the scalp. The eyes were normal except for a small hemorrhage in the fundus of the right eye; the disks were normal. The thyroid was not palpable. The lungs were negative. The heart was slightly enlarged to the left with an accentuated aortic second sound. The blood pressure was 210/140; pulse, 80. Abdominal palpation revealed no masses or tenderness. On pelvic examination the clitoris was normal, while the uterus was only about half normal size.

Laboratory Studies. On admission the blood count was as follows: erythrocytes, 5,300,000; hemoglobin, 102% (Sahli); leukocytes, 11,000; neutrophils, 67%; lymphocytes, 23%; monocytes, 10%. The reticulocytes were 2.1% and the platelets 448,000. The coagulation and bleeding times were normal. Urinalysis: the specific gravity ranged from 1.010 to 1.025; moderate albumin, no sugar. There was an occasional hyaline and granular cast.

Blood Chemistry. Blood urea nitrogen was 13, the fasting blood sugar 113 mg. per 100 cc. Although the urine was consistently sugar-free on the ward diet, she had a diabetic sugar-tolerance curve as follows:

	Blood sugar.	Urine sugar.
Fasting	113	0
½ hour after 100 gm. glucose	240	+
1 hour after 100 gm. glucose	330	++++
2 hours after 100 gm. glucose	320	++++
3 hours after 100 gm. glucose	242	++++
4 hours after 100 gm. glucose	185	++

The blood cholesterol was 390 mg. per 100 cc.; serum calcium, 10.4 mg. per 100 cc.; serum phosphorus, 3.4 mg. per 100 cc.; blood phosphatase, 32 units. Phenolphthalein test of kidney function showed 65% in 2 hours. The basal metabolic rate was +2%.

The electrocardiograph showed simple tachycardia and left-axis deviation. Orthodiagram showed the heart to be enlarged 17% above the predicted normal area.

The visual fields were normal.

Roentgen ray films of the pituitary fossa showed apparently normal measurements (8.5 by 6.5 cm.) but examination was considered not entirely accurate because of the degree of decalcification of the posterior clinoid process. This decalcification was also manifested in the bones of the calvarium, feet, pelvis and lower spine. Very marked arteriosclerosis was demonstrated by Roenten ray, in the arteries of the legs. There were multiple fractures of the ribs, although no history of trauma was obtained.

Gastro-intestinal Roentgen ray showed a distinctly abnormal small intestinal pattern characterized by an increase of tone and peristaltic rushes. A urogram revealed a normally functioning urinary tract in which there were no shadows or distortion of the kidney outline that suggested adrenal tumor.

The tentative diagnosis was Cushing's syndrome due to basophilic adenoma of the pituitary or to an adrenal cortical tumor. The outstanding features therefore were the onset of abdominal obesity in 1932 at the age of 25, followed by the progressive development of hirsutism, amenorrhea and hypertension until her admission on February 2, 1936. At this time generalized decalcification and diminished glucose tolerance were observed. There were no neurologic or routine Roentgen ray findings which served to differentiate the possible pituitary or adrenal tumor that was suspected.

Subsequent Course. On February 27, 1936, Roentgen ray therapy of the pituitary gland was instituted. Treatment, continued until March 15, 1936, gave a total dosage of 1000 r. She had one abortive menstruation at the time of the first treatment. Except for this there was no change whatever in her condition, and on April 21, 1936, she was transferred to the Surgical Service of Dr. E. L. Eliason. On April 22, 250 cc. of air were injected into the retroperitoneal spaces followed by Roentgen ray examination, according to the method of Cahill *et al.*[1] This revealed a possible adrenal tumor on the right side (Fig. 2).

Operation. April 27, 1936. The abdomen was explored through a right subcostal incision (Cahill *et al.*[1]). The left adrenal was not seen or felt, but the peritoneum on this side was not opened for exploration of the subperitoneal fat. After opening the posterior peritoneum on the right, the right adrenal was exposed. The residual emphysema from the air injection was an added source of difficulty at this stage. The right adrenal was found to contain a well-encapsulated mass measuring 3.5 by 3 by 3 cm. This was removed, leaving part of the right adrenal *in situ*. The usual postoperative measures including fluids, glucose and saline were employed.

Postoperative Course. After operation the patient developed a sustained fever of 102° to 104° F. which persisted until her death on the eighth day. With this elevation of temperature no sweating was noticed, although she perspired freely on returning from the operating room. In spite of this severe reaction she was comfortable and clear mentally, giving one a false impression as to her well-being. She was able to eat an adequate soft diet during this time. Because of her fever no metabolic studies were attempted, but her blood pressure showed a striking change. The most striking physiologic response to the removal of the tumor was the prompt fall of the blood pressure to a normal level. This was constant and sustained for 6 days, until the pre-mortal fall to the shock level occurred. This and the other findings during this period are summarized in Fig. 3. She went into shock and died on the eighth day after operation. The terminal serum chloride was 88 m Eq/L and the serum sodium 127 m Eq/L.

Autopsy. (Dr. O. Norris Smith; 4½ hours after death.) There was

FIG. 1.—Abdominal striæ and general configuration.

FIG. 2.—Roentgen ray of adrenal regions after air injection.

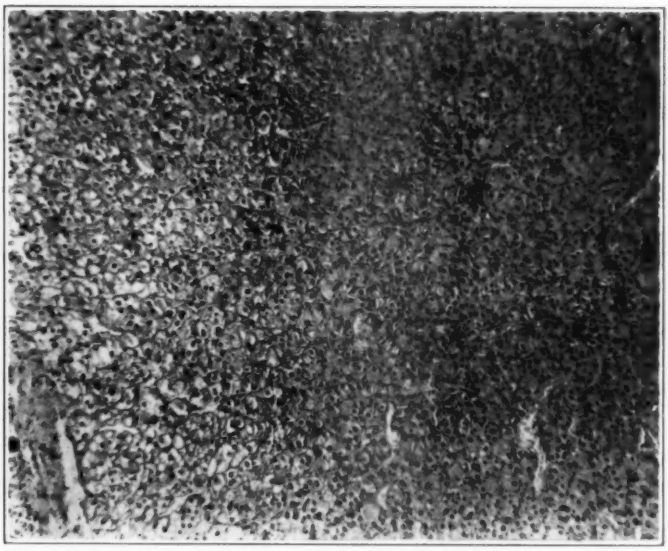

FIG. 4.—Adrenal cortical tumor (× 92).

massive adipose deposition in the viscera. The operative site and neighboring structures showed no signs of infection or hemorrhage, the only changes being the expected minor exudative reaction.

The *lungs* showed moderate bilateral atelectasis, due to the elevated diaphragm. The *heart* (380 gm.) was of normal size, but showed moderate left ventricular hypertrophy. The coronaries and endocardium showed slight atherosclerosis with no occlusion. The aorta was the site of diffuse, marked atherosclerosis without calcification or ulceration. The bones were thin, and easily broken or cut, suggesting diffuse osteoporosis. The *liver* (1860 gm.) was enlarged, soft and yellow in color. The extreme fatty change was determined chemically, the fatty acids being 35 gm. % (normal, 2 to 5%). The *spleen* (130 gm.) was slightly congested. The *pan-*

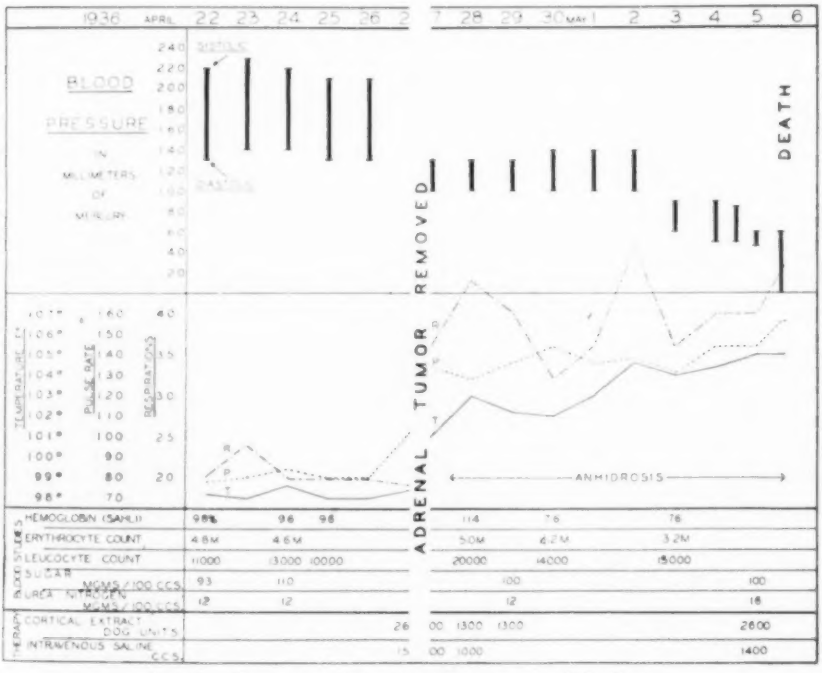

FIG. 3.—Summary of postoperative course and findings.

creas appeared normal in size but was distinctly more firm than normal. The *kidneys* showed an infiltration with yellow deposits similar to the liver and they were slightly granular. The *gastro-intestinal tract* was grossly normal.

Histologic Study. This showed in the *heart* intimal thickening without occlusion of the coronaries and hypertrophy of the muscle fibers. There was marked patchy atheromatous degeneration of the *aorta*. The *lungs* showed slight congestion and edema and a mild bronchiolitis in the left lobe. In the *liver* no normal cells were seen, the tissue consisting chiefly of large "seal ring" cells with moderate vascular engorgement. The arterioles of the *spleen* were thickened. In the *kidney* there was lipoid nephrosis and mild benign nephrosclerosis. The *bones* showed definite osteomalacia. Section of the *skin* revealed no localized lesion that accounted

for the striæ, although there was slight segmented thinning and atrophy of the corium.

Adrenals. The left adrenal could not be found despite careful dissection of the entire perirenal fatty tissue on that side. The remaining part of the right adrenal was grossly normal in structure but much smaller than usual. The upper portion contained the bed of the tumor which was filled with a small, clean clot. Microscopically, this adrenal cortex was rather pale, the zona reticularis being especially washed out. The medulla was prominent in one section, not discernible in others, and was probably not abnormal. The portions of the gland next to the bed of the enucleated tumor showed hemorrhage and necrosis. The gland was not weighed but was estimated to represent approximately half of a normal adrenal in size.

The Adrenal Tumor. Section showed a very cellular tumor that was well encapsulted (Fig. 4). There was very little stroma. The cells were of the cortical adrenal type. Their arrangement was orderly and similar to that seen in the zona fascicularis. The cells appeared to be mature and well-differentiated and contained abundant lipoid material. The nuclei were uniform in size and their relation to the cytoplasm was about the same in all cells.

In the *thymic* region no tumor or mass was demonstrable. The tissue removed for section showed only adipose tissue, with no trace of thymus remnants.

The *thyroid* gland was not enlarged. Microscopically, the thyroid tissue was pale, fairly cellular, the acini moderately filled with homogenous colloid separated from the acinar epithelium often by large clear vacuoles. There was no clear evidence of involution or hyperplasia. Marked arteriosclerosis was noted in the thyroid.

No *parathyroid* tissue was found in the thyroid or the capsule. The tissue outside the capsule was not exhaustively examined.

Pancreas. The predominant pathologic feature here was the extensive sclerosis of arteries and arterioles, many of the latter being plugged with dense fibrin. There was an extensive lobular fibrosis at places apparently completely destroying the acinar tissue but leaving clumps of islets, this process being more prominent in the head of the pancreas where the islets were very sparsely scattered. In the section from the tail of the pancreas fibrosis was minimal, while the islets were abnormally large, numerous and cellular.

The *uterus* was small (approximately 4 by 5 by 1.5 cm.). Histologic section showed an intact endometrium with short atrophic glands. The myometrium was extensively fibrotic.

The *ovaries* each measured about 3 cm. in greatest diameter. Microscopically, the interstitial stroma was abundantly cellular, the serosa normal. There were extensive patches of scar tissue. No primary or developing follicles could be found.

The *breasts*, while large from obesity, showed atrophy of the glandular elements histologically.

The *pituitary* (Dr. I. T. Zeckwer): The vessels of the brain were not markedly sclerosed. The pituitary was thought to be slightly enlarged in the lateral diameter. On careful review of serial sections no adenoma was found. The basophil cells seemed somewhat reduced in number. Some of the basophils contained intracellular hyaline material of the type described by Crooke[2] as occurring constantly in cases of Cushing's syndrome. In one section a few basophils had infiltrated the posterior lobe. The acidophils were numerous.

Discussion. The patient described represents an instance of an adrenal cortical tumor associated with the fully developed picture

TABLE 1.—ORDER OF FREQUENCY OF PRINCIPAL SYMPTOMS OF 55 PROVED CASES OF TUMORS OR HYPERPLASIA OF THE ADRENAL CORTEX (1917–1935), 45 FEMALES, 10 MALES.

	Virilism or hirsutism.	Amenorrhea.	Obesity.	Hypertension (150 mm.).	Glycosuria.	Striæ.	Decalcification.*	Increased M.B.M.*
Carcinoma or hypernephroma (30)	24	17	15	15	12	6	4	2
Adenomata (14)	12	8	6	7	5	5	3	1
Hyperplasia (11)	8	4	6	5	7	0	1	4
Total	44	29	27	27*	24	11	8*	7*
Per cent	80	65	49	49	44	20	15	13

* Not all cases examined for this abnormality.

of Cushing's syndrome. The incidence of the individual symptoms in 55 proved cases of adrenal tumor is summarized in Table 1. The unexplained elements in this case are especially the high postoperative fever without sweating for which no adequate cause can be assigned. It is possible that sweating was suppressed in an effort to conserve sodium chloride, but no such compensatory anhidrosis has been described in Addison's disease. The cause of death cannot be clearly stated. There was no evidence of infection or hemorrhage. Adrenal insufficiency is possible, but it is difficult to define the degree of this condition. In favor of adrenal insufficiency are: (*a*) The small and atrophic adrenal remaining on the right side; (*b*) the premortal fall in blood pressure; (*c*) the terminal blood chemistry. Questions arising in connection with this evidence are as follows: *A*. The amount of adrenal tissue remaining after operation would have supported an experimental animal. Thus, one-third of one adrenal maintains the appearance of health in the cat. *B*. The fall in blood pressure is compatible with any critical condition. *C*. The blood sodium and chloride were taken after salt administration and their original values may have been masked by this. However, the lowering of the sodium and chloride was not accompanied by the alterations in sugar and urea which might be expected on the eighth day of adrenal insufficiency. Furthermore, the extent of the electrolyte changes does not exceed that described by Sunderman, Austin and Camac[11] as occurring in pneumonia and other fevers. Whether this patient's high fever caused such changes or whether a tax upon adrenal function occurs in all fevers are points beyond speculation at present. Since there is no final answer to these questions, adrenal insufficiency is at least doubtful and the cause of death cannot be stated.

The absence of one adrenal has been reported by Miloslavich,[9] Dietrich and Siegmund,[4] and a few others, and once in a case of

cortical tumor by Feinblatt.[6] Three additional cases of absence of one adrenal have been found in the autopsy records of this hospital since 1894. None of these were associated with contralateral tumor.

A practical warning may be taken from the facts discussed. Before removal, inspect the side opposite the tumor. Following the removal of an adrenal cortical tumor, the blood should be carefully watched for the first signs of adrenal insufficiency. It may be that daily serum sodium determinations are necessary to do this, at least when the Cushing syndrome is present. The use of saline and cortical extract for 48 hours postoperatively is clearly indicated, as the majority of fatalities have occurred within that time. It is not possible to say how long such treatment should be continued, but the danger of adrenal insufficiency may not have passed in that short period. Of 40 cases of all tumor types operated upon, 19 died, although the recent mortality is less than this.

A few remarks may be made concerning the syndrome in general. The types of endocrine tumors causing all or part of this patient's picture have been described by others (Robb-Smith and Lescher[10]). The pathologic types of adrenal tumor have been reviewed.[1] The feature that has concerned us chiefly is the disturbance of carbohydrate metabolism. In this hospital it has been shown[7] that removal of the adrenals modifies pancreatic diabetes in the cat. This alleviated diabetes is expressed by a markedly decreased glucose, nitrogen and acetone body excretion compared to that in the depancreatized cat, as well as by an increased period of survival. The carbohydrate tolerance of these animals is not significantly increased and the results appear due to a diminution of the production of glucose and acetone bodies rather than to their normal utilization. A similar modification of phloridzin diabetes in the rat after adrenalectomy has been demonstrated by Evans.[5] It has also been shown[8a] that adrenotropic extract of the anterior pituitary aggravates the diabetes to a very slight degree when the adrenals are absent and to a marked degree in the hypophysectomized-depancreatized cat in which adrenals are present. The details of the action of pituitary extracts are not yet fully understood.

The type of patient herein reported represents the opposite situation in which an excessive secretion of the adrenal cortex, hitherto impossible to produce experimentally, impairs carbohydrate metabolism. It is not known whether the adrenals exert this effect directly or through the pituitary or some other endocrine gland. The frequency with which adrenal cortical tumors cause glycosuria or impaired carbohydrate tolerance is shown in Table 2. In this connection the relationship of adrenal hyperplasia and glycosuria in 20 proved cases of pituitary basophilism is also summarized (Table 3). From Tables 2 and 3 it is apparent that the adrenal cortex may play an important part in carbohydrate metab-

olism. The relation of the adrenal cortex to carbohydrate regulation is not yet understood. However, experimental work[85] suggests that this is not regulated by the "salt-and-water" hormone but by some other element, which may be an unknown hormone of the

TABLE 2.—CARBOHYDRATE METABOLISM OF 55 CASES OF PROVED TUMORS OR HYPERPLASIA OF THE ADRENAL CORTEX (1917–1935).

	Carcinoma or hypernephroma.	Benign adenomata.	Bilateral hyperplasia.	Total.	Per cent.
Number of cases	30	14	11	55	100
No impairment of carbohydrate metabolism demonstrated	16	8	4	28	51
No fasting glycosuria, but impaired carbohydrate utilization after glucose	2	1	0	3	5
Glycosuria present:					
(*a*) Transitory	3	1	1	5	9
(*b*) Well marked	9	4	6	19	35
Cases with impaired tolerance	..	..	..	27	49

cortex or may be an expression of an interrelationship between the adrenal and the pituitary. The finding of the hyaline change of Crooke[2] in the pituitary in this patient suggests the latter mechanism.

Summary. A case of adrenal cortical adenoma is reported in

TABLE 3.—INCIDENCE OF GLYCOSURIA IN PROVED CASES OF PITUITARY BASOPHILISM.

Number of cases.	Glycosuria.		Adrenal cortex.		
	Present.	Absent.	Normal.	Hyperplasia.	Not noted.
20	14 (70%)	6	4	11	5 (all had glycosuria)

INCIDENCE OF GLYCOSURIA IN RELATION TO THE STATE OF THE ADRENAL CORTEX.

	Number of cases.	Glycosuria.	
		Present.	Absent.
Cortex hyperplastic	11	8 (73%)	3
Cortex normal	4	1 (25%)	3

CONDITION OF THE ISLANDS OF LANGERHANS IN THE CASES EXHIBITING GLYCOSURIA.

Number of cases.	Islands of Langerhans.		
	Normal.	"Fatty."	Not noted.
14	6	2	6

which the diagnosis was confirmed by operation and autopsy. The left adrenal was absent. The patient presented all the classical features of Cushing's syndrome. There was no pituitary tumor, but the basophil cells showed the hyaline change of Crooke.

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THE EFFECT OF SPLANCHNIC NERVE RESECTION ON PATIENTS SUFFERING FROM HYPERTENSION.

By Irvine H. Page, M.D.,

ASSOCIATE MEMBER OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH,

AND

George J. Heuer, M.D.,

PROFESSOR OF SURGERY, CORNELL UNIVERSITY MEDICAL SCHOOL,

NEW YORK CITY.

(From the Hospital of the Rockefeller Institute for Medical Research, and the New York Hospital and Cornell University Medical School.)

Increased tone of the arteries in hypertension has been thought to be due, at least in part, either to increase in vasoconstrictor impulses acting on normal vessels or normal impulses acting on abnormally sensitive vessels. Since hypertension, similar to essential hypertension in man, has not been reproduced in animals, it has not been possible to test this hypothesis by experiment on them. The report of Craig and Brown[11] that resection of the splanchnic nerves caused arterial pressure to fall in patients suffering from essential hypertension, and that it did not appear to injure the patients, aroused our interest in the possibility of obtaining information on the participation of the sympathetic nervous system in the genesis and maintenance of elevated blood pressure.

The purpose of our investigation was to ascertain if possible the effect of splanchnic nerve resection and extirpation of the lower thoracic sympathetic ganglia on the immediate course of essential and malignant hypertension and on the special functions of the body, which one of us (I. H. P.) has been observing in connection with studies on the natural history of hypertension.

A considerable body of evidence, mostly physiologic in nature, indicates that the size of the vascular bed of the splanchnic region both in man and animals is important in the maintenance of arterial pressure (this evidence has been reviewed by Page and Heuer (1937)).[40b]

Most observers agree that the immediate cause of hypertension is narrowing of the peripheral arterioles.[20b] Observation of the

retinal arterioles and other vessels available for direct observation, such as those in the nail beds, lips, and conjunctiva, indicates that constriction is general. This has been further emphasized by the important experiments of Prinzmetal and Wilson[46] and Pickering.[44] They have shown that the blood flow in the forearm is the same in patients with hypertension as in normal persons. Were hypertension due to increased vascular resistance confined to some one area (splanchnic for example), the blood flow through the vessels in the rest of the body would be increased unless they too had contracted. If, on the other hand, the increased resistance is generalized and uniform, the blood flow in all parts of the systemic circulation will be the same as in normal persons—the high blood pressure simply overcoming the increased resistance in all areas. It is of interest to note, however, that the vascular lesions which are probably due to hypertension are usually limited to certain vascular areas. These lesions are notable in the kidneys, spleen and eyes, and we have repeatedly observed marked arteriosclerosis in the vessels in the meninges. These morbid vascular changes are almost wholly lacking in the great vascular bed of the muscles.[3,20a,38]

Participation of the Nervous System in Genesis of Hypertension. Opinion differs on participation of the nervous system in the genesis of the hypertonus responsible for hypertension. The following observations favor the belief that the nervous system is involved. In many cases of hypertension marked nervous and mental instability is observed, especially early in the course of the disease.[5,13,39b,41,47,55a,b] The close association of this instability and the appearance of hypertension has been frequently and justifiably stressed. It is well known that emotion produces rise in arterial pressure. Stimulation of various regions of the hypothalamus and cerebral cortex produces marked rise in blood pressure.[28,31,32,51] Injuries to the nervous system may be associated with development of hypertension.[6] Essential hypertension appears to be limited to man and chiefly to those men living under so-called "civilized conditions." In animals, hypertension that appears to be of nervous origin can be produced either by denervation of the carotid sinuses[34] or by injection of kaolin into the cisterna magna.[16] Spinal anesthesia abolishes all vasoconstrictor impulses and consequently lowers blood pressure. The fall often is proportionately greater in patients with hypertension than in those with normal pressure.[14] Section of anterior spinal nerve roots causes a sharp and prolonged fall in arterial pressure.[2] Injuries in which a transverse lesion of the cord has occurred in hypertensive patients have been followed by marked reduction in arterial pressure.

Vascular Hypertonus May Exist in the Absence of Central Nervous Connections. Evidence that vascular hypertonus in hypertension is due to an intrinsic property of the vessel wall is less extensive but nevertheless impressive. It consists of the observation that heat

applied to the body or anesthetization of the vasomotor nerves to the arm does not lead to a greater increase in the blood flow through the forearm in hypertensive than in normal subjects.[44, 46] If hypertonus had been due to increased vasoconstrictor impulses a greater increase in rate of blood flow should have occurred in hypertensive patients than in normal subjects. It may be objected that the viscera respond to removal of nervous control in a fashion different to that of the forearm. At least one important visceral organ behaves, however, somewhat similarly. It has been found that denervation of the kidneys does not appreciably increase urea clearance, and hence probably not the blood flow, in patients with essential hypertension.[40a] The parallelism between urea clearance and renal blood flow was shown by Van Slyke, Rhoads, Hiller and Alving,[54] in normal dogs. Had hypertonus been due to impulses of central origin a marked rise in the rate of blood flow might have been anticipated. Page and Heuer[40b] found no change in urea clearance or ability to concentrate urine, even after the extensive denervation of the kidneys produced by section of the anterior spinal nerve roots from the sixth thoracic to the second lumbar segments. Actual stripping of the renal pedicle of nerves in patients suffering from Bright's disease with hypertension was also without effect on the blood flow. It was concluded that the polyuria and increased activity of the denervated kidney observed in acute animal experiments did not occur in man.* This evidence appears to indicate that the hypertonus of the vessels of the kidneys, if such there be, is not primarily of nervous origin.

It seems impossible, on the basis of contemporary evidence, to decide whether hypertonus of the vessels in hypertension is of nervous origin. Clinical evidence favors the belief that the nervous system actively participates, whereas evidence gathered by experimental methods favors the opposite belief. It does not appear improbable that the two views may be reconciled when knowledge of the mechanism of hypertension is more comprehensive.

Fall in arterial pressure is known to occur after severing the central connection of a portion of the sympathetic nervous system in patients suffering from hypertension. The phenomenon is consistent with either belief. In case the neurogenic view is urged, the fall in arterial pressure may be taken to depend upon prevention of *abnormal* tonic impulses from impinging upon *normal* vascular musculature; and when the vascular genesis is held, the fall may be

* The explanation for the discrepancy between these observations and the classic physiologic experiments on animals is probably to be found in the work of Klisiecki, Pickford, Rothschild and Verney.[33] They showed that the close parallelism in the rate of flow and in the compositions of the urine from the two kidneys of normal dogs remained unaffected by tightening a thread around the splanchnic nerves. Inequality in the rate of flow from the innervated and denervated kidneys immediately appeared when the dog, after recovery from the operation of left splanchnic resection or denervation of the left kidney, was again put under the influence of a general anesthetic.

explained by prevention of *normal* tonic impulses from reaching *abnormally* sensitive vascular musculature.

Certain Problems Raised by Denervation Procedures Intended to Lower Arterial Pressure. One of the most important problems is whether with fall of arterial pressure adequate blood supply will be provided vital organs such as the kidneys? It was shown by Page[39a] that marked reduction in arterial pressure may occur in patients when the fall in pressure is not sudden without change in urea clearance and, correspondingly, in blood flow. There was therefore no reason to believe that reduction in arterial pressure adversely affected the function of the kidneys. As shown especially by Freeman,[22] and Freeman, Shaw and Synder,[23] the chief function of the vasomotor nerves appears to be to modify the volume flow of the blood in accordance with the needs of the body as a whole. After removal of this control by sympathectomy, blood flow is then determined largely by the metabolic demand of the local tissues.

Since denervation must perforce be performed in limited areas of the body other problems are raised which require careful study. It may be reasoned that abolition of nervous impulses in one area of the body would lead to local vasodilatation, whereas the vessels of the remainder of the body would remain constricted, leading to insufficient blood flow. Actually it has been observed that when arterial pressure falls, relaxation at least of the vessels in the eye-ground occurs. The fact that relaxation occurs in vessels other than those which have been denervated may be in part responsible for the observed fall in blood pressure following operation. Nor have any signs or symptoms been noted on clinical examination of the patients that would lead to the belief that blood flow had become inadequate in other organs.

Another problem, one of great practical importance, is whether reduction of arterial pressure by means of denervation in patients suffering from hypertension is maintained. Experiments by Magnus[36] on animals with normal blood pressure indicate that section of the splanchnic nerve leads to fall in pressure which lasts for days or weeks but then returns to the pre-operative level.

Removal of the entire sympathetic chain causes only a temporary lowering in arterial pressure which soon returns to normal according to Cannon.[8] Grimson[26] states that complete sympathectomy will not permanently alter blood pressure of normal dogs longer than 94 to 225 days. The pressure after sympathectomy remains at a higher level than would be expected after withdrawal of all vasoconstrictor tone (*e. g.*, by spinal anesthesia). From this observation, Wilson, Roome and Grimson[56] suggest that the function is taken over by a peripheral vasoconstrictor mechanism. Studies by Page and Heuer[40b] on patients subjected to section of the anterior nerve roots (Adson-Brown operation) demonstrated that in some of the patients the return of arterial pressure to its high level occurred

within a month or more, whereas in others it was far below the preoperative level after $2\frac{1}{2}$ years. The tendency was for a slow but definite rise in pressure level to occur. Unless return of hypertonus is very prolonged, it constitutes a serious objection to denervation procedures as therapeutic measures.

Experiments performed on animals with normal arterial pressure in which the splanchnic nerves were severed have offered little guidance in similar operations on patients with hypertension. Goldblatt, Gross and Hanzal[25] found that splanchnic resection neither prevented the development of hypertension nor cured it when renal ischemia was produced in dogs by constricting the renal arteries. Freeman and Page[23a] were also able to *produce* hypertension in dogs in which the entire sympathetic nervous system had been removed by this method. Sympathectomy combined with denervation of the heart did not abolish the hypertension produced by Goldblatt's method. The evidence, conclusive as it is, however, is of limited value in connection with operation in man, because it is not known whether hypertension in dogs produced by renal ischemia resembles essential or nephritic hypertension.

Although most evidence is opposed to the view that the adrenal glands are directly responsible for essential hypertension, it should be mentioned that these glands are at least partially denervated by section of the splanchnic nerves (Anrep[4] for example) though not completely (Cannon, Lewis and Britton).[9] Denervation does not prevent liberation of epinephrine by humoral stimulants such as acetylcholine, histamine or peptone (Siehe).[50] Consequently, it is not possible, on the basis of contemporary evidence, to draw conclusions regarding the secretion of epinephrine in patients with hypertension following splanchnic resection.

Lastly, it must not be overlooked that smooth muscle deprived of its nerve supply in chronic experiments in animals is more sensitive to epinephrine than when normally innervated.[18,37] More recently Freeman, Smithwick and White[24] have shown that the recurrence of vascular spasm after complete sympathectomy in human extremities is probably due to sensitization of the extremity to epinephrine. Degeneration of the parasympathetic supply to smooth muscle also sensitizes smooth muscle to acetylcholine.[49] The evidence thus indicates that denervated smooth muscle is sensitized to the natural chemical mediators of the nerve impulses which cause it to contract. Furthermore, Cannon and Rosenblueth[10] have shown that preganglionic denervation of *sympathetic ganglia* makes them more sensitive to stimulation by acetylcholine. Sympathetic ganglion cells may be regarded as innervated by preganglionic fibers. Whether such sensitization phenomena play an important part in the results of operations designed to reduce arterial pressure by means of denervation is not known.

Partial answers to these problems of varied nature are to be found in the evidence of experimental nature referred to in each case. It is obvious, however, that in the last analysis the answers depend upon careful and prolonged observation of patients. The record of each patient is therefore set forth in some detail in this study, since some of the questions which have been raised appear to be readily answered by this means.

Splanchnic Nerve Resection in Man. Probably the first to suggest splanchnic nerve resection as a treatment for hypertension were Daniélopolu,[12] Bruening and Stahl[7] and Pende[42] in 1923. Jean[30] had previously recommended it for relief of pain of gastric crises. Pieri,[45] Durante[17] and Santucci[48] reported on 4 patients subjected to operation. The data which were published are so meager that one cannot be certain of the results of the operation. Craig and Brown[11] studied some of the effects of both unilateral and bilateral resection much more carefully in 5 cases. The infradiaphragmatic approach to the nerves was employed and after section of them, the lumbar sympathetic chain was broken by removal of the first or second lumbar ganglion. Symptomatic relief was often observed, but arterial pressure was not reduced sufficiently to consider the procedure of marked therapeutic value. They showed conclusively that the operation was a relatively safe procedure and was not followed by any untoward effects. They believed that it might be of value in the early stages of the severe progressive form of essential hypertension in young persons.

The operation has been subsequently taken up by a number of surgeons, notably by Peet. Detailed studies of their cases have not as yet appeared. Fralick and Peet[21] reported operations on 90 patients. The results have been observed in 36 cases from 5 to 22 months after operation: 5 were symptom-free and maintained normal blood pressure; 2 showed resolution of the morbid changes in the fundus due to malignant hypertension and 1 patient disappearance of angiospastic retinitis; 18 showed an appreciable drop in blood pressure and the pressure in 13 was unaffected.

The operation has been performed for other purposes than reduction of arterial blood pressure. de Takats and Cuthbert[15a,b] reported that it increases the sugar tolerance particularly of juvenile diabetics. Temporary but marked effect of the operation in preventing the appearance of hemoglobinuria following chilling of the feet of a patient suffering from paroxysmal hemoglobinuria were observed by Ernstene and Gardner.[19]

Management of Patients. Blood pressure measurements were made at 9.30 A.M. daily with the patients in bed. During the pre-operative period of observation, which consisted of a month or more, they were not allowed out of bed for any purpose. After operation the patients were allowed up at will, but blood pressure measurements were made while they were in bed, hence the measurements cannot be regarded as strictly comparable with

those made before operation. Sedatives, including chloral hydrate, amytal and, less often, sodium bromide, were employed sparingly before and seldom after operation. Diets were unrestricted as to quality or amount.

Clinical Observations. Renal efficiency was measured by urea clearance in the modified form described by Van Slyke, Page, Hiller and Kirk,[53] and by the ability of the kidneys to concentrate urine. The urea clearance was employed, not only because it is a delicate test, but because Van Slyke, Rhoads, Hiller and Alving[54] have shown that in dogs it parallels the renal blood flow. The specific gravity was measured on a 12-hour specimen voided at the end of 24 hours without fluids. Were protein present in sufficient amount to contribute to the specific gravity, a correction was made for it, that is, 0.003 subtracted from the total specific gravity for each 1% of protein (Lashmet and Newburgh[35]). The number of formed elements in the urine was estimated by the technique of Addis.[1] Not more than 500,000 red blood cells are excreted by persons with normal kidneys. The urine protein was measured by the method of Shevky and Stafford, as slightly modified by MacKay (Peters and Van Slyke[43]). The amount of plasma proteins was ascertained by the method of Howe.[29] Hemoglobin was measured by the Van Slyke and Neill[52] oxygen capacity method.

In some of the case histories the term "hypertensive diencephalic syndrome" is employed. By this is meant a syndrome often observed in patients suffering from hypertension consisting in its severest form of blushing which is usually confluent on the face and blotchy over the upper chest, slight perspiration over this area, lachrymation, palpitation, hypermotility of the intestine and slight rise of blood pressure (Page[39b]). Salivation may be observed. Similar states are observed in the absence of hypertension, yet its frequent occurrence during it suggests some close association. The syndrome has been called "diencephalic" because it resembles the clinical manifestations following stimulation of the diencephalon by tumors or drugs.

Explanation of Charts. On the charts the mean normal of each value represented is drawn as a base line; the shaded areas between the base line and the points representing observations indicate the degree of deviation above or below the average normal. The brackets at the left of the scales for urea clearance, urine concentration and hematuria, indicate the range of normal variability. The normal base line for hemoglobin varies with the patient's age and sex; the base line for each patient is located at the mean normal level for his age and sex (Table 39, p. 542; Peters and Van Slyke[43]). Blood pressure measurements were made daily at 9.30 A.M., but are represented in the charts as averages. Each dot usually represents the average of from 3 to 5 blood pressure measurements. The black areas representing edema have the following significance: Height of black area in quarters of total space, 1, trace; 2, moderate pitting; 3, marked pitting; 4, general edema with ascites. Morbid changes in the eyegrounds are recorded as follows: 1, Constriction of the arterioles; 2, arteriosclerosis; 3, exudate; 4, hemorrhages; and 5, papilledema. The estimated time elapsing between onset of the disease and admission to the hospital is recorded on the lowest line of the chart, as the first number following the word "months." The other numbers in the bottom row indicate months after first admission.

Operation. The operation of splanchnic nerve resection used in this series of cases consisted in the bilateral resection of segments of the great, small and, if present and found, the smallest splanchnic nerves together with the three lower dorsal ganglia. The operative approach is above the diaphragm and is similar to that used by Peet. Under general anesthesia a vertical incision 12 to 14 cm. long and parallel with the spine is made at the lateral border of the long muscles of the back, the mid-point of the incision lying over the previously identified eleventh rib. The incision is carried

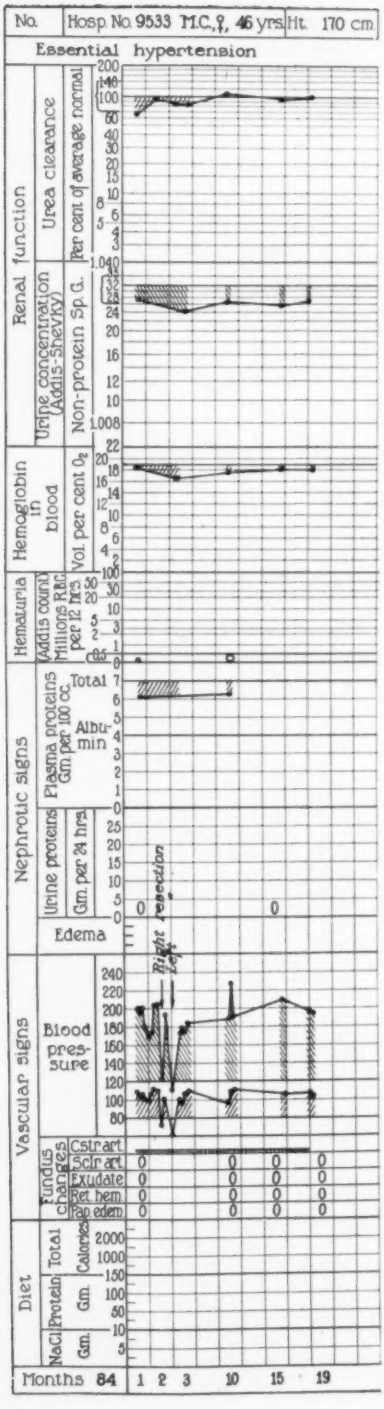
through the fibers of the serratus muscle and the underlying fascia covering the long muscles of the spine. These are lifted from the ribs and retracted toward the mid-line. The eleventh rib is exposed and a segment approximately 6 cm. long next to the spine is resected. The intercostal muscles are carefully raised from the underlying pleura and those between the tenth and twelfth ribs divided. The pleura is carefully separated from the bodies of the vertebræ and retracted and as the dissection is carried more deeply toward the anterior margin of the vertebral column, the lower dorsal ganglia are first brought into view lying upon the anteriolateral surface of the vertebral bodies and at a deeper level the great splanchnic nerve. The latter is grasped, dissected free to the point where it penetrates the diaphragm, and a segment often 6 to 8 cm. long is resected. In the course of this dissection the small splanchnic, and occasionally the smallest splanchnic nerve, are identified together with the sympathetic fibers connecting them with the lower dorsal sympathetic ganglia. The ganglia together with the small splanchnic nerve are freed and are removed. In no instance has there been any untoward bleeding and the wounds have invariably been closed with silk without drainage.

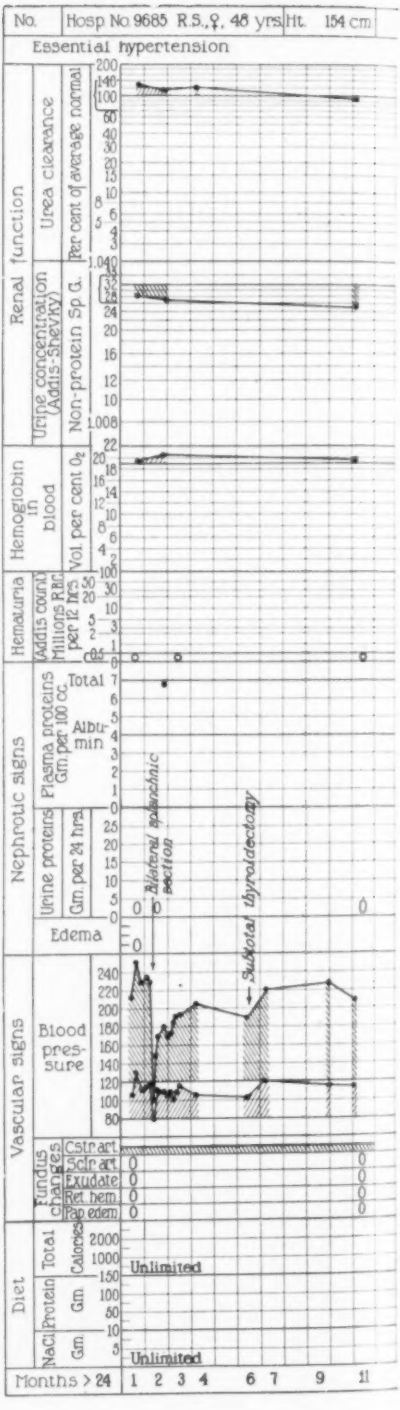
Of the 9 patients included in this report, the bilateral operation was performed at one sitting in 5, at two sittings in 3. In 1 patient a right splanchnic resection only was performed. On 1 patient a small tear in the pleura occurred in the course of the procedure but resulting slight pneumothorax failed to provoke any untoward symptoms. With the exception of one instance of postoperative pleural effusion, there were no postoperative complications, and in all cases the wounds healed *per primam*.

Case Reports. Case 1 (No. 9533). This patient, a 46-year-old housewife, complained of precordial pain for the past 7 months. Hypertension has commonly occurred in members of her family. An abortion was performed 9 years ago, but since then she has borne children. Temperamentally she is excitable, impulsive, often very irritable and worries over unimportant things. In the past few years she has noticed that urticaria appears on her skin when she becomes nervous. She cries easily and without apparent cause. Her memory is not nearly so accurate as formerly. She has had frequent headaches for many years. She tires easily. Precordial pain is often brought on by excitement and is said to be relieved by nitroglycerine. Menstruation became irregular 5 years ago, and stopped 2 years ago. Her blood pressure was found normal 9 years ago but was elevated a year later during her first pregnancy. Two years later arterial pressure varied from 185/95 to 220/125 mm. Recently, the subjective symptoms have become so severe that she has been incapacitated. She was kindly referred to us by Dr. Maurice T. Root of West Hartford, Conn.

Physical examination showed that she was a thin, high-strung woman appearing chronically ill. The eyegrounds were normal. Tonsils had been cleanly removed. Heart rate was 88. A soft systolic murmur was heard at the apex. Peripheral vessels were thickened (Grade 1). Roentgen ray examination showed the cardiac silhouette to be normal. The electrocardiogram was normal.

Although there appeared to be a large neurotic element associated with hypertension in this patient, the arterial pressure did not fall under complete bed rest and mild sedatives. During a month of observation it varied from 212 to 166 mm. systolic and 120 to 100 mm. diastolic. The average pressure was 190/110 mm. Since no significant relief from the subjective symptoms had been secured it seemed desirable to ascertain the effects of bilateral splanchnic resection.


No. Hosp No. 9533 M.C., ♀, 46 yrs. Ht. 170 cm.
Essential hypertension
Renal function
Urea clearance
Per cent of average normal
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
Hemoglobin in blood
Vol. per cent O2
Hematuria
Addis count Millions R.B.C. per 12 hrs.
Nephrotic signs
Plasma proteins Gm. per 100 cc.
Total
Albumin
Urine proteins
Gm. per 24 hrs.
Edema
Vascular signs
Blood pressure
Right
Left
Fundus changes
Cstr art
Sclr art
Exudate
Ret. hem
Pap edem
Diet
Total Calories
Protein Gm.
NaCl Gm.
Months 84
1 2 3 10 15 19


No. Hosp No. 9685 R.S., ♀, 46 yrs. Ht. 154 cm.
Essential hypertension
Renal function
Urea clearance
Per cent of average normal
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
Hemoglobin in blood
Vol. per cent O2
Hematuria
Addis count Millions R.B.C. per 12 hrs.
Nephrotic signs
Plasma proteins Gm. per 100 cc.
Total
Albumin
Urine proteins
Gm. per 24 hrs.
Edema
Bilateral splanchnic section
Subtotal thyroidectomy
Vascular signs
Blood pressure
Fundus changes
Cstr art
Sclr art
Exudate
Ret. hem
Pap edem
Diet
Total Calories
Protein Gm.
NaCl Gm.
Unlimited
Unlimited
Months > 24
1 2 3 4 6 7 9 11

On June 19, 1935, right supradiaphragmatic splanchnic resection was performed and left supradiaphragmatic splanchnic resection on July 1. Except for some stiffness of the muscles of the back, the postoperative course was uneventful. Blood pressure varied rather widely for a few days after operation, but became stabilized at an average of 178/110 mm. during the 21 days rest in the hospital after operation. It varied from 190 to 168 mm., systolic; and 118 to 96 mm., diastolic. The subjective symptoms were moderated but did not disappear. Headaches and precordial pain were much less severe, but emotional instability continued unabated. Arterial pressure 1½ years later was about the same as before operation. She felt somewhat better in that she was less nervous and had fewer headaches.

Summary of Case 1. A woman aged 46 with essential hypertension probably beginning during her first pregnancy 8 years ago, exhibited many signs and symptoms of a highly developed neurosis. Splanchnic resection lowered arterial pressure temporarily, but within 6 months it has resumed its pre-operative level. The arterial pressure was about the same 1½ years later but headaches were less frequent, precordial pains had disappeared and she tired less easily. It was our opinion that she had been aided mentally by the operation without marked physical change.

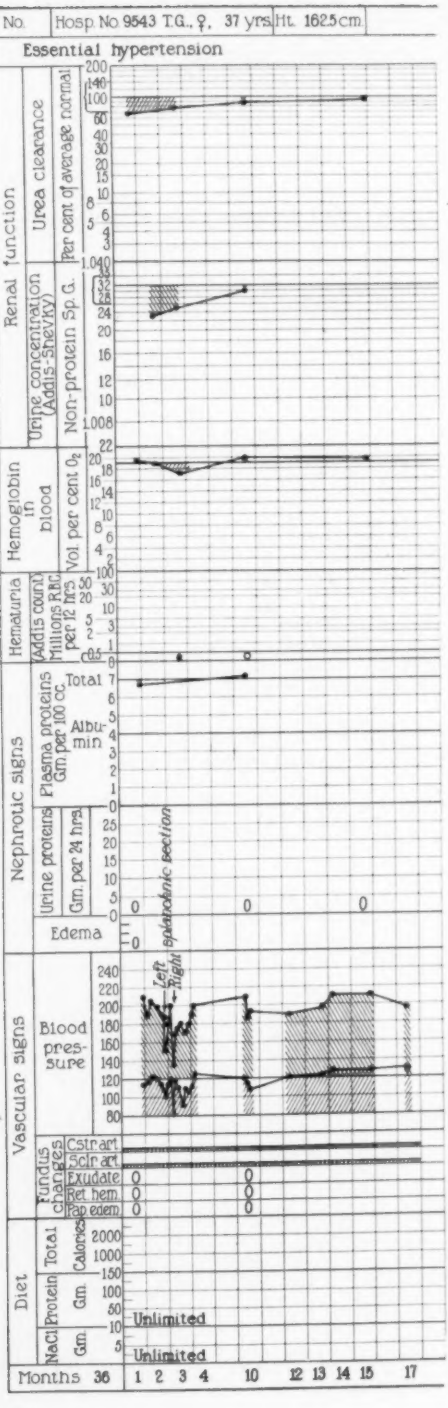
Case 2 (No. 9685). This patient, a 48-year-old Swiss housewife, complained of nervousness and irritability. Her past health was always excellent. She had hot flashes, spots before her eyes, cried and blushed easily. Her menstruation was regular, but was always rather scanty. She noticed no change in it.

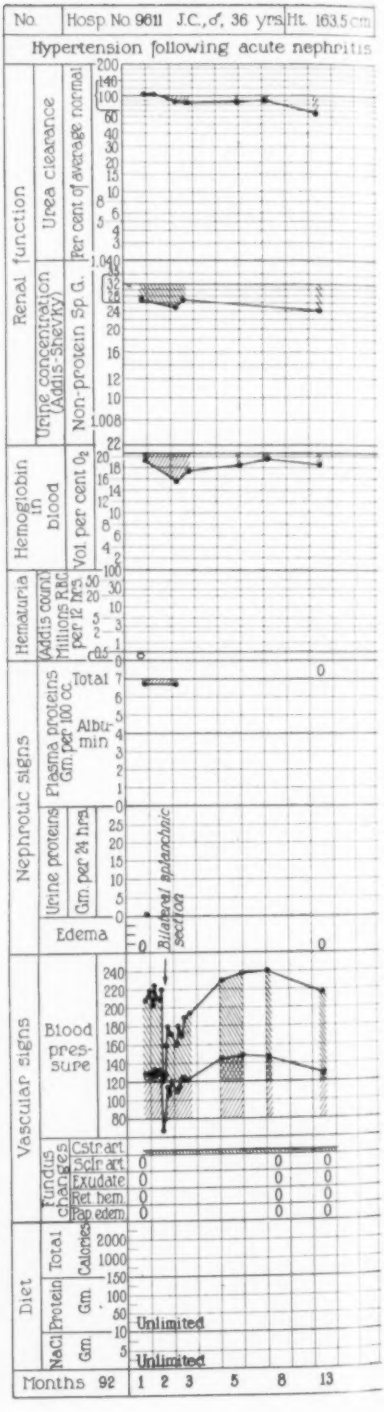
On physical examination she was found to be very overactive. There was a marked flush over her face and the skin of her face and hands and feet was moist. The arterioles of the fundi showed Grade 2 constriction and no perivasculitis. They were not tortuous. The veins was dilated (Grade 2) with very slight if any arteriovenous compression. The thyroid gland was diffusely enlarged (Grade 1). The heart was very slightly enlarged (Grade 1). There were no murmurs; A_2 and P_2 were not accentuated. Peripheral vessels were not thickened. Superficial and deep reflexes were hyperactive. Roentgen ray of the skull showed Grade 1 pineal calcification and a small but normal sella. The blood pressure ranged from 260 to 210 mm. systolic, and 130 to 106 diastolic, with an average pressure of 230/120 mm.

On December 14, 1935, bilateral supradiaphragmatic splanchnic resection was performed. Except for some abdominal distention and difficulty in voiding, the postoperative course was uneventful. Within 10 days the patient was up and about. The basal metabolic rate before operation was +24; 2 weeks after operation it was −9. There was no change in renal efficiency. Her nervousness continued. Blood pressure varied from 160 to 194 systolic and 96 to 120 diastolic. The average was 180/110 mm. during the period of hospitalization of 1 month, but 9 months after operation it has risen to 220/122 mm.

Five months after operation the symptoms and signs of adenomatous goiter were sufficiently marked to justify subtotal thyroidectomy. One month before this operation the basal metabolism was +22 and it fell to +6 2 weeks after operation. No significant change in arterial pressure occurred. She appeared to be less restless.

Summary of Case 2. This 48-year-old woman suffered from essential hypertension and adenomatous goiter. Renal function


No. Hosp No 9543 T.G., ♀, 37 yrs. Ht. 162.5 cm.
Essential hypertension
Renal function
Urea clearance
Per cent of average normal
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
Hemoglobin in blood
Vol. per cent O_2
Hematuria
Addis count
Millions R.B.C. per 12 hrs.
Nephrotic signs
Plasma proteins Gm. per 100 cc.
Total
Albumin
Urine proteins
Gm. per 24 hrs.
Edema
Vascular signs
Blood pressure
Left
Right
Bilateral splanchnic section
Fundus changes
Cstr art.
Sclr art.
Exudate
Ret. hem.
Pap. edem.
Diet
Total Calories
Protein Gm.
NaCl Gm.
Unlimited
Unlimited
Months 36
1 2 3 4 10 12 13 14 15 17


No. Hosp No 9611 J.C., ♂, 36 yrs. Ht. 163.5 cm.
Hypertension following acute nephritis
Renal function
Urea clearance
Per cent of average normal
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
Hemoglobin in blood
Vol. per cent O_2
Hematuria
Addis count
Millions R.B.C. per 12 hrs.
Nephrotic signs
Plasma proteins Gm. per 100 cc.
Total
Albumin
Urine proteins
Gm. per 24 hrs.
Edema
Bilateral splanchnic section
Vascular signs
Blood pressure
Fundus changes
Cstr art.
Sclr art.
Exudate
Ret. hem.
Pap. edem.
Diet
Total Calories
Protein Gm.
NaCl Gm.
Unlimited
Unlimited
Months 92
1 2 3 5 8 13

was normal. One year after splanchnic resection and 9 months after subtotal thyroidectomy, arterial pressure was unchanged from its pre-operative level. She is less nervous than before thyroidectomy, but otherwise there has been little change in her clinical condition.

Case 3 (No. 9543). A 37-year-old housewife, complained of weakness, excessive nervousness, insomnia and palpitations for 2½ years. She was irritable, impulsive and worried much. She blushed and cried often without apparent reason. Since the onset of the present illness there was a decrease in menstrual flow.

The present illness was first recognized 3 years ago. She noticed swelling of the ankles during the fifth month of her first pregnancy. Two months later she had a miscarriage. Her blood pressure was said to be elevated and protein was found in the urine. Hypertension has persisted.

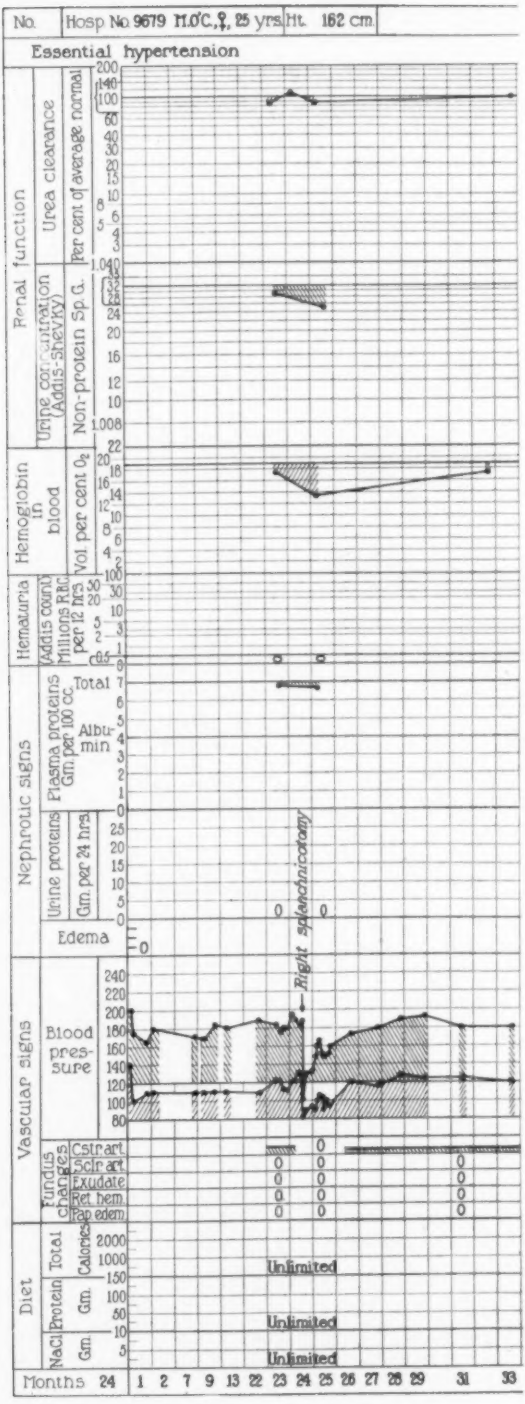
The patient was a small, nervous woman, appearing very restless. The disks of the eyegrounds were slightly hyperemic (Grade 1) the arterioles were slightly tortuous (Grade 1) and in a number of places there was slight arteriovenous compression. The thyroid gland was not palpable. The heart was not enlarged and the sounds were of good quality. There was a fine tremor to the outstretched fingers, but no other signs of Graves' disease. The deep reflexes were overactive but equal, on both sides. Roentgen ray revealed that the sella turcica was normal. The basal metabolic rate was +25% on admission and +25% 16 days later. The blood pressure varied from 220 to 184 systolic and 140 to 104 diastolic, and averaged 200/120 mm. during 23 days of rest in bed. The Wassermann reaction was negative.

On June 28, 1935, splanchnic resection was performed. The postoperative course was uneventful. For a period of 3 to 4 months she felt better; symptoms and signs of the "hypertensive diencephalic syndrome" continued unchanged. One year after operation the arterial pressure averaged 194/114 mm. and she again complained of palpitations, restlessness and extreme nervousness.

Summary of Case 3. This 37-year-old woman suffered from essential hypertension. It may have begun during her first pregnancy. The disease appears to be quite benign. Bilateral splanchnic resection was associated with a moderate fall in arterial pressure and a feeling of well-being which lasted only a few months. Now 1½ years after operation, the pressure is at its pre-operative level and restlessness, nervousness and palpitations have returned.

Case 4 (No. 9611). This 35-year-old man complained of dizzy spells, palpitations and shortness of breath on exertion for 3 months. He suffered possibly from acute nephritis with slight hypertension 8 years ago. Arterial pressure 8 months ago was found to be 240/138 mm.

The patient was found to be a short, thin, wiry man not appearing ill. The arterioles of the fundi were constricted (Grade 1), but there was no perivascular reaction or tortuosity. The tonsils were chronically inflamed. The heart was not enlarged; its rate was regular but rapid with a soft blowing systolic murmur at the apex. Peripheral vessels were thickened (Grade 2). The sella turcica appeared normal to Roentgen ray. The systolic pressure varied from 226 to 200; the diastolic from 140 to 116 mm.; average, 210/130 for a month's period. This patient appeared well suited for operation since no renal damage was present, cardiac enlargement had not occurred and the retinal changes were minimal.


No.
Hosp No 9679 M.O'C., ♀, 25 yrs. Ht. 162 cm.
Essential hypertension
Renal function
Urea clearance
Per cent of average normal
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
Hemoglobin in blood
Vol per cent O2
Hematuria
Addis count Millions R.B.C. per 12 hrs.
Nephrotic signs
Plasma proteins Gm. per 100 cc.
Total
Albumin
Urine proteins
Gm. per 24 hrs.
Edema
Vascular signs
Blood pressure
Right splanchnicotomy
Fundus changes
C.str art.
Scl art.
Exudate
Ret. hem.
Pap. edem.
Diet
Total Calories
Protein Gm.
NaCl Gm.
Unlimited
Unlimited
Unlimited
Months
24
1 2 7 9 13 22 23 24 25 26 27 28 29 31 33

Bilateral supradiaphragmatic splanchnic resection was performed on October 17, 1935. Convalescence was uneventful. Arterial pressure after a marked fall slowly rose to an average of 182/118 (systolic 194 to 170 mm.; diastolic 124 to 110 mm.) during a period of 4 weeks. One year after operation the average pressure was 218/130. He no longer complains of dizzy spells or palpitations, but he becomes fatigued very easily.

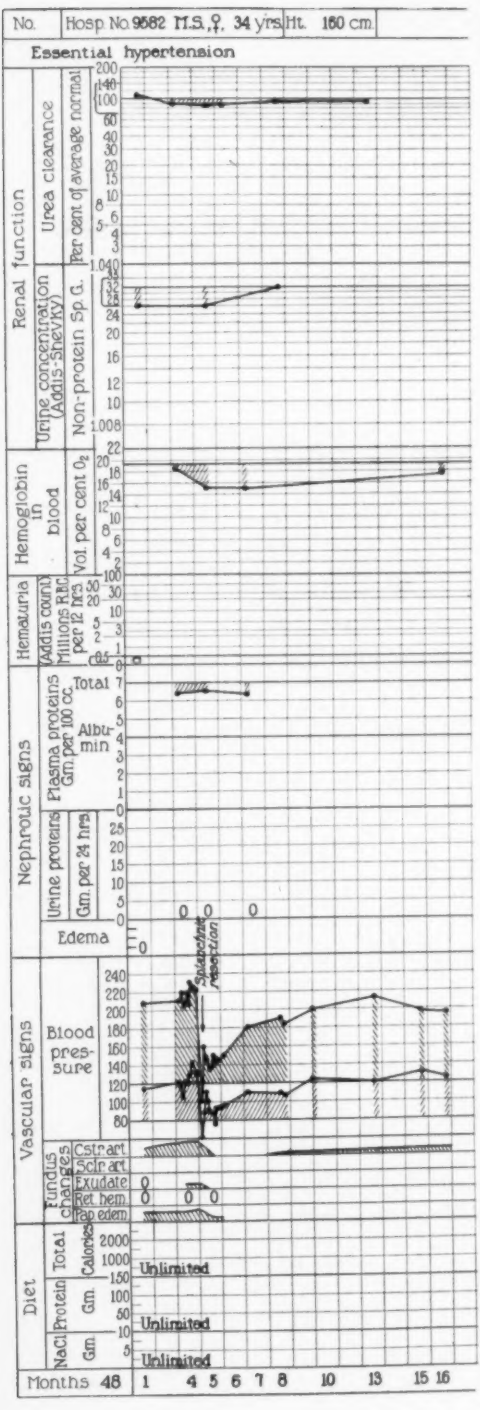
Summary of Case 4. This 35-year-old man had essential hypertension with slight morbid vascular change and normal renal efficiency. Splanchnic resection caused a fall in arterial pressure which lasted for 2 months. It then regained its original level. The operation does not appear to have influenced the course of the disease.

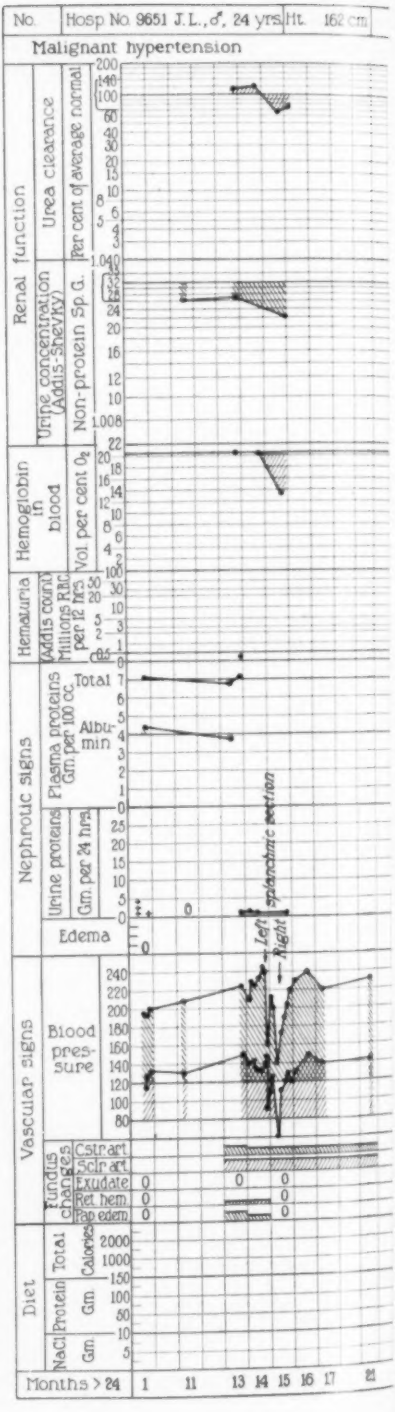
Case 5 (No. 9679). A 25-year-old telephone operator complained of severe headaches for the past 3 years. She had always been well until the present illness, except for scarlet fever at 4 years of age and typhoid at 16. Appendectomy was performed 9 years ago, and tonsillectomy 6 months ago. She was impulsive and irritable, and easily fatigued. In the past 3 years, she noticed that she cried spontaneously and also that blushing was marked. Menstruation was scanty but regular. She was oversexed. Five years ago, it was known that her blood pressure was normal; 3 years ago it was found to be slightly elevated and 1 year ago was found to be 200/140. She noticed that in the past 5 months on climbing one flight of stairs she became short of breath. Her ankles have not swelled.

Physical examination showed that the patient was highly nervous. The skin over the face and upper chest was covered with perspiration and there was a mottled blush over this area. The arterioles of the ocular fundi showed sausage-shaped constriction (Grade 2) with slight perivascular reaction (Grade 1). There was arteriovenous compression (Grade 2) in certain places. The veins were not unusual and there were no hemorrhages or exudates. There was a marked carotid pulsation in the neck. The thyroid gland was diffusely enlarged (Grade 1) but it was soft and there were no nodules. The heart rate was 80 to 92 and there was a short systolic whiff at the apex. The aortic second sound was markedly accentuated. Roentgen ray of the chest showed the total transverse diameter of the heart 11.2 cm., the internal chest diameter 25.5 cm. There was moderate elongation of the aorta without widening. A Roentgen ray photograph of the skull showed that the calvarium was moderately thickened and there was especially heavy calcification over the frontal bones. There was apparent erosion of the posterior clinoid process. The pituitary gland itself was not encroached upon. The pineal gland was calcified (Grade 1). The cold pressor test showed a response of 28 mm. systolic and 12 mm. diastolic. The blood pressure varied from 206 maximum to 170 minimum systolic, and maximum diastolic of 126, minimum 106. The average pressure was 180/120, over a period of 1 month in bed. The basal metabolism was -2.6%.

Splanchnic nerve resection was performed on the right side. The nerve was found to be unusually large. The convalescence was uneventful and within 6 days she was up and about. The blood pressure was somewhat lower; during the period of 24 days after operation it varied from 140 to 170 systolic, and 90 to 108 diastolic (mean pressure, 160/100). Within 3 months the arterial pressure had returned to its pre-operative level. Headaches have been reduced in intensity and frequency (10 months after operation) and this appears to have been the only benefit derived from operation.

Summary of Case 5. This 25-year-old patient suffered from mild essential hypertension of 2 years' duration. Headaches and easy


No.
Hosp No. 9582 M.S., ♀, 34 yrs. Ht. 160 cm.
Essential hypertension
Renal function
Urea clearance
Per cent of average normal
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
Hemoglobin in blood
Vol. per cent O_2
Hematuria
Addis count
Millions RBC per 12 hrs.
Nephrotic signs
Plasma proteins Gm. per 100 cc.
Total
Albumin
Urine proteins
Gm. per 24 hrs.
Edema
Vascular signs
Blood pressure
Splanchnic resection
Fundus changes
Cstr art
Sclr art
Exudate
Ret hem.
Pap edem
Diet
Total Calories
Protein Gm.
NaCl Gm.
Unlimited
Unlimited
Unlimited
Months 48
1 4 5 6 7 8 10 13 15 16


No.
Hosp No. 9651 J.L., ♂, 24 yrs. Ht. 162 cm.
Malignant hypertension
Renal function
Urea clearance
Per cent of average normal
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
Hemoglobin in blood
Vol. per cent O_2
Hematuria
Addis count
Millions RBC per 12 hrs.
Nephrotic signs
Plasma proteins Gm. per 100 cc.
Total
Albumin
Urine proteins
Gm. per 24 hrs.
Edema
Left splanchnic section
Right
Vascular signs
Blood pressure
Fundus changes
Cstr art
Sclr art
Exudate
Ret hem.
Pap edem
Diet
Total Calories
Protein Gm.
NaCl Gm.
Months > 24
1 11 13 14 15 16 17 21

fatigability were the most marked symptoms. Unilateral splanchnic resection reduced the arterial pressure temporarily, but within 3 months it returned to the pre-operative level. The only benefit derived from operation appeared to be reduction in the frequency and intensity of the headaches.

CASE 6 (No. 9582). A 34-year-old Italian housewife complained of headaches for about 10 years. They have become very severe and occur almost every day. Five years ago her second baby was born, and during the last months of pregnancy she developed edema, which disappeared after delivery. She was told that she had hypertension at that time. She noticed palpitations for the first time 4 years ago. In the past 2 years, signs and symptoms characteristic of the "hypertensive diencephalic syndrome" have become increasingly prominent. She is overexcitable, irritable and worries greatly.

The eyegrounds showed moderate papilledema. The arterioles were constricted, in many places to the point of complete obliteration, and the veins were dilated (Grade 3). There were no hemorrhages nor exudate. The thyroid gland was diffusely enlarged (Grade 1) but no other physical signs of hyperthyroidism were found. There was a marked systolic thrust in the jugular notch. The heart rate was very rapid. The sounds were of good quality and there were no murmurs. The electrocardiogram showed the *T*-wave upright in Lead I, and inverted in Leads II and III. Conduction time was 0.12 seconds. Sinus tachycardia was present and also intraventricular heart block. Roentgen ray examination showed the sella turcica to be normal. The basal metabolic rate 4 months ago was +33, and at present it is +32 as measured on two occasions. The cold pressor test showed a rise of 8 mm. systolic and 12 mm. diastolic. The blood pressure varied from 192 to 232 mm. systolic and 112 to 144 mm. diastolic, the average pressures being 216/126 mm. during 26 days in bed.

Bilateral supradiaphragmatic splanchnic resection was performed on November 5, 1935. Postoperative convalescence was uneventful, except for a small left pleural effusion directly following the operation. On the tenth day the patient was up. There was a rather remarkable change in the fundi. Papilledema had markedly regressed. The arterioles were of normal caliber. There was no arteriovenous compression. The veins were of normal size. There was no exudate or hemorrhage. The blood pressure averaged 150/90 over a period of 5 weeks after operation with a systolic maximum of 170 and minimum of 138; diastolic maximum was 106, minimum 78. Within 5 months the blood pressure returned to the pre-operative level. The frequency and severity of the headaches were much reduced for a period of 1 year after operation. The eyegrounds remained normal during that period.

Summary of Case 6. This patient suffered from moderately severe essential hypertension. The most remarkable feature of the case was the occurrence of papilledema and severe arteriolar constriction in the eyegrounds. Following operation, after a fall lasting several months, the blood pressure level returned to very nearly the pre-operative level. In spite of this, the morbid fundus changes disappeared and after 1 year the eyegrounds were still normal. Moderate subjective improvement occurred.

CASE 7 (No. 9651). A 25-year-old salesman had epileptic attacks for 2 years, and about twice a month since then. It is impossible to date the onset of his hypertension. It was found at the time of onset of the epilepsy. Headaches were the only symptom and these were not severe.

Physical examination showed papilledema of both nerve heads. The disks were hyperemic and the edges blurred. The arterioles in many places were markedly constricted. Many of the arterioles showed corkscrew distortion. There was sclerosis (Grade 4). The veins were dilated and there was arteriovenous compression (Grade 4). Temporal to the right disk was a small hemorrhage. The tonsils had been removed. The heart was boot-shaped. There appeared to be slight widening at the base. There was an aortic diastolic murmur. Peripheral vessels were slightly thickened. Deep reflexes were hyperactive.

Roentgen ray of skull showed that the pineal gland was calcified (Grade 1); the sella was normal. Roentgen ray of the chest showed the aorta to be widened and the lungs normal. The electrocardiogram showed that the *T* waves in Leads I and II were inverted. Arterial pressure varied from 240 mm. to 204 mm. systolic and 140 mm. to 122 mm. diastolic (average 226/134 mm.) during a period of 21 days in bed.

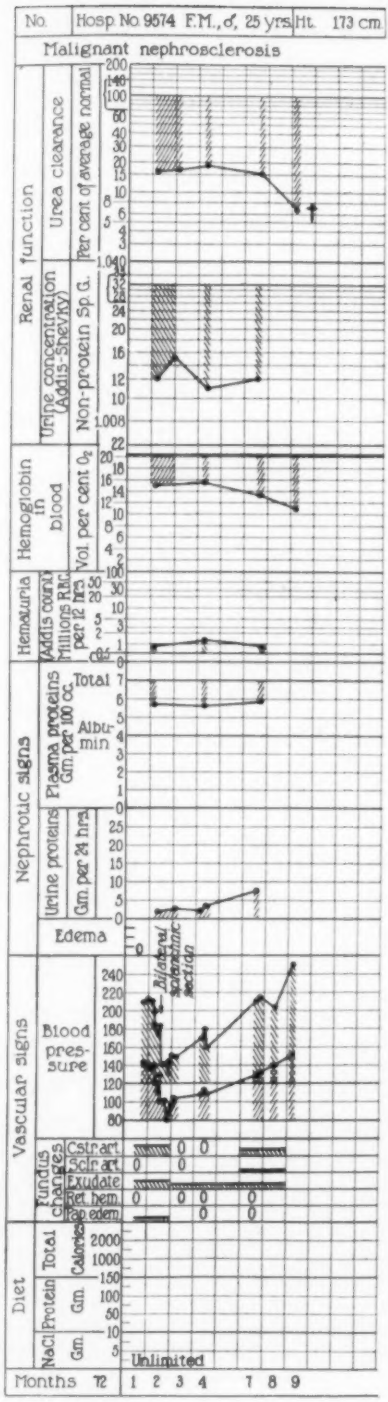
On November 26, 1935, left splanchnic resection was performed. There was no change in his average blood pressure following operation. On December 10, right splanchnic resection was performed. The operation was complicated by postoperative hemorrhage, which necessitated reopening of the wound, but following this the course was not remarkable. There was a marked fall in hemoglobin to 13.54 vol.%, and a very slight fall in urea clearance. Arterial pressure varied from 109 to 235 mm. systolic and 110 to 140 diastolic (average 200/130 mm.) during a period of 38 days in bed. Within 2 months, the pressure had reached the pre-operative level. He had two attacks during the convalescence suggestive of epilepsy.

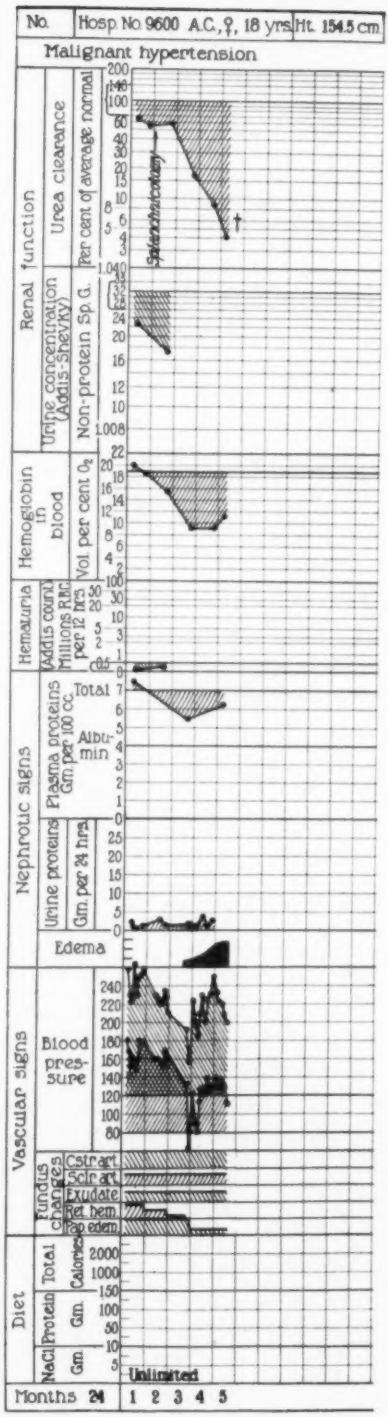
Summary of Case 7. This was a case of early malignant hypertension in a 25-year-old man, complicated by epilepsy. Bilateral splanchnic resection produced a temporary sharp fall in arterial pressure but within 2 months it had regained its pre-operative level. During the month following operation the papilledema disappeared. The symptoms and signs of the epilepsy were unchanged.

Case 8 (No. 9574). A 25-year-old male clerk, complained of headaches for 2 months. He had always considered himself healthy. In 1931, tonsillectomy was performed. He noticed recently that he cries without reason, and often has palpitations of the heart. There has been slight dyspnea on exertion. At the age of 17, his blood pressure was said to have been a little elevated, but he paid no attention to this, and it was not until 8 years later that it was again measured because of rather constant headaches. It was found to be moderately elevated.

Fundus examination showed Grade 1 papilledema of the right disk as well as Grade 1 hyperemia. The arterioles in both eyes were constricted (Grade 3); but certain of them showed only slight constriction. In some places there was rather marked arteriovenous compression. The veins were dilated (Grade 2). Diffusely scattered throughout the retinæ, but especially concentrated in a ring around the disk were small, discrete patches of hard white exudate. There were no hemorrhages. The thyroid gland was just palpable. The heart sounds were of good quality. Peripheral vessels were definitely thickened (Grade 2 to 3). The blood pressure varied from 182 to 210 mm. systolic and 120 to 140 diastolic (average 198/136 mm.). The electrocardiogram showed that the *T* waves were diphasic in Lead I, upright in Lead II, and diphasic in Lead III; conduction time was 0.19 seconds. The rhythm was normal. The sella turcica was normal as shown by Roentgen ray photographs. The Wassermann and Klein reactions were negative.

It was our impression that this was a case of rapidly advancing, malignant nephrosclerosis. Since his physical condition was excellent, except for the


No.
Hosp No 9574 F.M., ♂, 25 yrs.
Ht. 173 cm.
Malignant nephrosclerosis
Renal function
Urea clearance
Per cent of average normal
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
Hemoglobin in blood
Vol. per cent O_2
Hematuria
Addis count
Millions R.B.C. per 12 hrs.
Nephrotic signs
Plasma proteins Gm. per 100 cc.
Total
Albumin
Urine proteins
Gm. per 24 hrs.
Edema
Vascular signs
Blood pressure
Fundus changes
Cstr art.
Sclr art.
Exudate
Ret. hem.
Pap. edem.
Diet
Total Calories
Protein Gm.
NaCl Gm.
Bilateral splanchnic section
Unlimited
Months
1 2 3 4 7 8 9


No.
Hosp No 9600 A.C., ♀, 18 yrs.
Ht. 154.5 cm.
Malignant hypertension
Renal function
Urea clearance
Per cent of average normal
Urine concentration (Addis-Shevky)
Non-protein Sp. G.
Hemoglobin in blood
Vol. per cent O_2
Hematuria
Addis count
Millions R.B.C. per 12 hrs.
Nephrotic signs
Plasma proteins Gm. per 100 cc.
Total
Albumin
Urine proteins
Gm. per 24 hrs.
Edema
Vascular signs
Blood pressure
Fundus changes
Cstr art.
Sclr art.
Exudate
Ret. hem.
Pap. edem.
Diet
Total Calories
Protein Gm.
NaCl Gm.
Splanchnicotomy
Unlimited
Months
1 2 3 4 5

low renal efficiency, it was believed that reduction of the elevated arterial pressure might prolong life.

Bilateral splanchnic resection was performed on July 11, 1935. Following operation small pleural effusions occurred, but these soon disappeared. Six weeks later, moderate regression of the fundus changes had occurred, but there was no improvement in renal function. Arterial pressure varied from 170 to 190 mm. systolic and 106 to 118 mm. diastolic. Six months after operation the pressure had returned to its original level and retinal changes were again present. Two months later death occurred from renal and cardiac failure.

Summary of Case 8. This 25-year-old man suffered from malignant hypertension with markedly reduced renal function. In spite of this, his general clinical condition was excellent, and he was almost without symptoms. Since arterial pressure was high and apparently causing morbid vascular changes, bilateral splanchnic resection was performed in an effort to reduce the pressure. Reduction occurred for a period of 3 months and definite regression of the pathologic changes in the eyegrounds was observed. Renal efficiency did not improve. Within 6 months, the arterial pressure rose to its pre-operative level and the disease resumed its progress ending with renal and cardiac failure 7 months after operation.

Case 9 (No. 9600). An 18-year-old girl considered herself healthy until 2 years ago when severe headaches began. Shortly thereafter, she had a convulsion. Her blood pressure was measured and found to be 140 mm. Headaches became more severe and were associated with nausea and vomiting. They were often followed by attacks suggesting epilepsy. Tingling in the hands and feet was noted, shortly followed by stiffening of the muscles of the body. She became stuporous and moderately cyanotic. The attack was usually terminated by vomiting. Arterial pressure taken shortly after it was 290/186 mm. on one occasion. The attacks usually appeared during the week preceding menstruation and seldom occurred until the next period. Recently they have increased in frequency. Now they may occur at any time. She has never had any signs or symptoms suggestive of the "hypertensive diencephalic syndrome."

Physical examination showed her to be well-developed and not appearing ill. Very marked papilledema was observed in both disks. The arterioles were irregular and showed moderate perivascular reaction (Grade 2). In many places they were obliterated. In some sectors the small arterioles were surrounded by hemorrhages. Hard white exudate occurred in small patches throughout the fundi. In the left fundus there was an early stellate figure. The heart was slightly enlarged (Grade 1).

Roentgen ray picture of the skull showed that the sella was flattened and bridged across. Spinal fluid pressure was 220 mm. of water, and arterial pressure was 232/160 mm. Blood and spinal fluid Wassermann reactions were negative.

She had a number of attacks such as those described above while in the hospital. It was difficult to be certain that the rise in arterial pressure was paroxysmal in nature because pressure measurements could be taken only at the termination of the attack after she had undergone severe physical strain. During the pre-operative period of observation arterial pressure averaged 242/160 mm.; systolic range, 264 to 210 mm.; diastolic 186 to 146 mm.

On October 1, 1935, bilateral splanchnic resection was performed. Throughout the operation the blood pressure remained markedly elevated. This was an unusual occurrence as all of the other patients showed marked reduction.

Convalescence was rapid and uneventful. Eighteen days after operation she suffered an attack strongly suggestive of a transient apoplexy. Right-sided weakness of the hand and foot appeared and she was unable to speak. This passed off in about an hour. Retinal changes were more marked than before operation and she complained of blurred vision. Arterial pressure averaged 230/158 mm. for a month after operation.

She was readmitted 2 months after operation, in the meantime having had an attack of acute cardiac failure and become totally blind. Papill-edema was extreme with almost complete obliteration of the arterioles. It appeared that the blood supply to the retina had been choked off. All signs and symptoms pointed to cardiac and renal failure. She died 4 months after operation.

Autopsy (Dr. C. P. Rhoads, 3 hours after death) confirmed the clinical diagnosis. The kidneys in particular showed marked morbid changes. The intima of the arterioles was extremely thickened leading almost to occlusion. The glomerular basement membrane was uniformly very marked thickened. Some increase in vascular endothelial nuclei was observed. Diffuse increase in interstitial connective tissue had occurred. The tubules were atrophied and dilated.

A plum sized tumor was found in the region of the right adrenal. Its appearance on microscopic examination was typical of a neuroblastoma. Trichloroacetic acid and aqueous extracts of the tumor were prepared and tested on anesthetized cats for epinephrine. None was found, though control extracts prepared from the patient's adrenal glands showed large amounts.

Summary of Case 9. This 18-year-old girl suffered from malignant hypertension which ran its course in 2 years. The disease was characterized by the early appearance of renal and cardiac failure and blindness. Bilateral splanchnic resection appeared to have no influence upon the course of the disease or its signs and symptoms.

Summary. 1. Splanchnic nerve resection with interruption of the thoracic sympathetic chain was performed on 9 patients. Six of them were cases of essential hypertension varying in severity from mild to severe and in age from 25 to 48 years. Of the other 3, 1 (aged 25) suffered from early malignant hypertension and the remaining 2 (aged 18 and 25) from severe malignant hypertension.

2. Splanchnic nerve resection was well borne in all patients, and there have been no complications or fatalities. We have been unable to detect that the patients have been harmed by the operation. The reduction in arterial pressure which occurred following operation was marked but within 6 months it had returned to the pre-operative level in all patients. Subjective improvement consisting of lessening in frequency and severity of headaches, ease of fatigue, nervousness, tenseness and irritability, occurred in 6 of the patients with essential hypertension, but in 3 improvement lasted less than a year. Improvement in those with malignant hypertension was transient.

3. Renal efficiency was unaffected by the operation. It also appeared to have no marked effect on the heart as judged by electrocardiographic records or Roentgen ray photographs (Table 1). No consistent change was observed in the pressor response to immersion of the hand in cold water (Hines and Brown test[27]). In 1 case of essential hypertension and 2 cases of malignant hypertension papilledema disappeared but reappeared in the latter cases within several months. Reduction in intensity of the constriction in the retinal arterioles occurred in all of the cases except 1 with malignant hypertension (similar cases are reported by Fralick and Peet[21]) demonstrating that arteriolar relaxation occurs in regions other than those denervated. In most of the patients constriction has returned after several months.

4. The therapeutic results in this small but representative group of cases do not appear to us to be encouraging.

TABLE 1.—ELECTROCARDIOGRAPHIC AND CARDIAC SHADOW RECORDS OF PATIENTS BEFORE AND AFTER SPLANCHNIC RESECTION.

Case No.	Time in weeks before and after operation.	Electrocardiogram.				Time in weeks before and after operation.	Measurement of heart on Roentgen ray plate.	
		T_1.	T_2.	T_3.	Conduction time, in seconds.		Transverse diameter, cm.	Internal diameter of chest, cm.
1	6 before	+	+	+	0.19	3	11.6	24.7
	32 after	+	+	+	0.16	52	11.4	23.3
2	3 before	+	+	−	0.15	3	12.5	24.3
	32 after	+	+	−	0.15	..	12.4	24.4
3	3 before	+	+	+	0.18	6	12.0	22.4
	60 after	+	+	+	0.14	..	13.2	23.5
4	3 before	+	+	+	0.12	3	10.6	23.5
5	2 before	+	+	+	0.14			
	20 after	+	+	−	0.13			
6*	12 before	+	−	−	0.15	2	12.2	23.5
	40 after	+	−	−	0.12	40	12.5	23.0
7	3 before	−	−	+	0.15	3	15.5	32.0
8	3 before	±	+	±	0.19	1	14.5	26.5
	22 after	±	+	+	0.15	22	14.8	26.9
9	1 before	+	+	+	0.15	2	10.2	23.5
	8 after	+	+	+	0.10	8	14.1	25.7

* Intraventricular heart block present.

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BOOK REVIEWS AND NOTICES.

PHYSICAL THERAPEUTIC METHODS IN OTOLARYNGOLOGY. By ABRAHAM R. HOLLENDER, M.D., F.A.C.S., Associate in Laryngology, Rhinology, and Otology, University of Illinois College of Medicine; Fellow of the American Academy of Ophthalmology and Otolaryngology. Pp. 442; 189 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, $5.00.

THE author is to be congratulated on both his presentation and choice of collaborators. The literature on otolaryngology of today is so filled with references to certain types of physical therapy that intelligent reading demands some knowledge of these procedures. In this book all such methods are clearly explained and an attempt has been made to evaluate their worth. A complete bibliography is included which will be of great help to the busy otolaryngologist who wishes to secure more detailed information upon any particular one of the subjects discussed.

K. H.

THE MANAGEMENT OF OBSTETRIC DIFFICULTIES. By PAUL TITUS, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh; Consulting Obstetrician and Gynecologist to the Pittsburgh City Homes and Hospital, Mayview, and to the Homestead Hospital, Homestead, Pa. Pp. 879; 314 illustrations, including 4 color plates. St. Louis: The C. V. Mosby Company, 1937. Price, $8.50.

THIS new work, representing an effort to aid practical physicians in meeting and contending with obstetric emergencies, proceeds at once concisely to the recognition and treatment of abnormal conditions. The book opens with an interesting discussion of the present trends in obstetric practice and problems of the day, such as maternal welfare, training of students and physicians in obstetrics, the trend toward specialization in practice and the increasing hospital service in many areas.

The text begins with an excellent discussion of the causes and factors and treatment of sterility which is followed by a section on the difficulties in diagnosis of pregnancy. Following chapters on the complications of pregnancy, labor and puerperium and obstetric operations, the accidents, injuries and abnormal conditions of the newborn are discussed. The book closes with 4 chapters on general topics: the preparation for obstetric operations, the pre-natal, postpartum, postoperative care of the obstetric patients, a separate chapter on the various forms of obstetric analgesia, anesthesia, technique of each and a final chapter on supportive treatment describing various types of intravenous injections and the technique of blood transfusion.

Titus reports 49.2% of pregnancy in his cases of relative sterility. His impression of treatment by means of hormonal extract is that the effect is uncertain, the underlying basis not clearly understood, the cost prohibitive, and distinct harm may result in some instances. The author regards the treatment of varicose veins during pregnancy as unnecessary except in rare instances. He does not favor myomectomy during pregnancy, but would perform the operation after Cesarean section on account of the frequent occurrence of necrobiosis. He supports Porro Cesarean section for generalized peritonitis as a result of a complicating appendicitis. Under the treatment of syphilis he states, "Syphilis in the pregnant woman should be treated as vigorously as in the non-pregnant woman." There

are many workers who feel that the treatment should consist only in a sufficient effort to prevent the child from being born a congenital syphilitic. The author expresses an extremely radical opinion on the treatment of hydatid mole and chorioepithelioma.

The author recommends breaking up the breech even before full dilatation occurs, but does not follow this by any effort of traction. Braxton-Hicks version is recommended for placenta prævia in the home. Very careful analysis of the individual case in the hospital should determine which of the described treatments is to be chosen. The use of blood transfusion in various hemorrhage conditions is stressed. Emphasis is placed on the recognition of contracted pelves as the basis of proper management of labor in such instances. The subject of pelvimetry, clinical and roentgenologic, is thoroughly presented as is also the management of dystocia from contracted pelvis.

Obstetric operations are described in detail with good accompanying illustrations. The low cervical section is preferred and the author mentions that both in this and classical section it is his practice uniformly to pack the uterus, using the De Lee shuttle with gauze attached. In his consideration of puerperal infection, the author describes the technique used in his hospital and makes the statement that complete masking of all patient contacts and the vaginal instillation of antiseptics has reduced his maternal morbidity from 18.9 to 8.92%. His well-known theories and treatment of hyperemesis gravidarum and toxemia of late pregnancy are succinctly set forth.

Space forbids a discussion of the author's personal opinions as to many other obstetrical complications. His teaching and technique should be of interest, not only to the general practitioner in quickly available directions in any emergency, but to the hospital chief who may wish to compare his preferences under such circumstances with those here so clearly and tersely set forth. P. W.

MODERN UROLOGY. In Original Contributions by American Authors. Vol. I. General Considerations—Diseases of Penis and Urethra—Diseases of Scrotum and Testicle—Diseases of Prostate and Seminal Vesicles. Vol. II. Diseases of the Bladder—Diseases of the Ureter—Diseases of the Kidney—Radiation Therapy of Tumors of the Genito-urinary Tract. Edited by HUGH CABOT, M.D., LL.D., C.M.G., F.A.C.S., Professor of Surgery, The Mayo Foundation, Graduate School of the University of Minnesota, and Consulting Surgeon to The Mayo Clinic, Rochester, Minn; formerly Dean and Professor of Surgery in the Medical School of the University of Michigan, Ann Arbor, Mich. Pp., Vol. I, 951; Vol. II, 862. Illustrations: Vol. I, 546 and 12 plates (some in colors); Vol. II, 374 and 9 colored plates. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $20.00.

THE last edition of this encyclopedic work appeared 12 years ago. So many changes have taken place that the present edition is practically a new work, to which 35 American authors have contributed. The first volume deals with general considerations, such as methods of diagnosis in lesions of the urinary tract, the use of the cystoscope, and syphilis of the genito-urinary organ, and with the diseases of the penis, the urethra, the scrotum, testicle, prostate and seminal vesicles. In the second volume are discussed the bladder, the ureters, kidneys, and the tumors of the genito-urinary tract. To illustrate the scope of the work, the contents of the section on the kidney may be cited: there are chapters on the embryology, anatomy, physiology and function of the kidney; on modern tests of renal function; on anomalies of the kidney, hydronephrosis, movable kidney, injuries to the kidneys; infections (including separate chapters on

schistosomiasis, renal ecchinococcosis, and tuberculosis), stones in the kidney and ureters, and of tumors of the kidneys.

Each chapter is profusely illustrated by well-selected photographs, diagrams and drawings, many of the later being remarkable for their combination of artistic excellence and strict adherence to anatomical detail.

It need scarcely be stated that these books are an invaluable reference work for the general practitioner, as well as a working tool for the specialist.

B. L.

St. Thomas's Hospital Reports, Second Series, Vol. I. Editors: Prof. O. L. V. S. De Wesselow, Mr. C. Max Page, assisted by Mr. N. R. Barrett, Dr. J. St. C. Elkington, Dr. A. J. Wrigley. Pp. 199; illustrated (3 in color). London: St. Thomas's Hospital, 1936. Price, 7s. 6d.

This, the "senior Borough hospital" of London, was the first—by a few months—to issue a volume of reports, 100 years ago. After various vicissitudes, the reports in 1870 began a single volume annually which latterly "have mainly consisted of arid statistical tables." The present volume is the first of a new type "which will aim in a series of original articles at a reflection of recent work carried out in the Hospital." It will be interesting to see how well and how long it can survive the inevitable trend of the staff members to present their best work in the recognized journals of wider distribution. If the excellence of the 20 articles that comprise the first volume is maintained, its success should be assured.

E. K.

Urological Roentgenology. By Miley B. Wesson, M.D., Ex-President, American Urological Association, and Howard E. Ruggles, M.D., Roentgenologist to the University of California Hospital, St. Luke's Hospital and Clinical Professor of Roentgenology, University of California Medical School. Pp. 269; 227 illustrations. Philadelphia: Lea & Febiger, 1936. Price, $5.00.

This book fulfills its intended purpose; that is, "to meet the needs of the physician who wants to learn to interpret urograms, be he urologist, roentgenologist, general practitioner or interne." It is an excellent, compact and fairly complete treatise on roentgen diagnosis of urologic disease. It maintains the high standards of the previous writings of its authors.

The text, which is concise yet fairly comprehensive, includes a brief history of urography and a discussion of the necessary equipment as well as the technique for retrograde study of the urinary tract. Indications and contraindications for the retrograde and the intravenous methods of study are presented. A discussion of the roentgenologic appearance of the normal urinary tract is followed by chapters concerned with the Roentgen and clinical diagnosis of disease processes and anomalous conditions which affect the urinary tract.

Because of the extensive source of films and case histories, supplied by members of the American Urological Association, this book presents many unusual roentgenograms. The chapter on congenital anomalies of the kidney and ureter is particularly interesting from the standpoint of the more uncommon Roentgen appearances. The chapters concerned with the discussion of hydronephrosis, tuberculosis, stones and tumors are well planned and each preceded by an outline of its contents. A generous bibliography is included.

The physical properties of the book are such that it is easy to read. The paper is of good quality, the print large and sharp and the illustrations of the roentgenograms are unusually clear.

G. C.

DISEASES OF THE NAILS. By V. PARDO-CASTELLO, M.D., formerly Assistant Professor of Dermatology and Syphilology, University of Havana; Member of the American Dermatological Association, etc. With a Foreword by HOWARD FOX, M.D., Professor of Dermatology and Syphilology, New York University, University and Bellevue Hospital Medical College. Pp. 177; 94 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, $3.50.

A SEARCHING monograph on diseases of the nails, like many another monographic study of obscure items in dermatology, is badly needed. This brief work is unquestionably affected by the relatively small amount of research heretofore devoted to minor but nonetheless essential appendages of the human skin. The work therefore follows the conventional anatomical, pathologic and clinical classificatory lines, and probably perforce gives relatively little attention to function. It is an admirable descriptive catalogue, reënforced by really superb photography, and should enable the practising skin specialist to attach a name to practically any named condition of the nails now recognized. To this extent, also, it will serve the general practitioner and diagnostician, inasmuch as it illustrates the nail involvement associated with a variety of systemic conditions.

In therapeutics the work is practically restricted in scope to irradiation therapy with Roentgen ray, an unfortunate state of affairs, as much a commentary upon a limited outlook in the field of dermatology as it is any fault of the author. It must be conceded, on the other hand, that at least for temporary, and in some cases lasting results, Roentgen therapy of nail conditions is practically the most effective sole or adjunct therapy that we have.

The bibliography is short, conditioned by the subject and the mode of approach; the index is satisfactory.

This work is a step in the right direction. It is to be hoped that it will be followed by longer steps made possible by improved knowledge of the terrain as well as a better definition of monographic objectives.

J. S.

CLASSIFICATION OF YEASTS AND YEAST-LIKE FUNGI. By C. VIRGINIA FISHER, PH.D., on Fleischmann Grant for Mycological Investigation, and LLOYD ARNOLD, M.D., Professor of Bacteriology and Public Health. Pp. 92; 10 plates. Urbana, Ill.: University of Illinois Press, 1936. Price, $1.00.

FIRST is taken up the history and classification (both morphologic and biochemical) of yeasts in general. In succeeding sections, yeast infections of special regions (vagina, mouth, gastro-intestinal tract, skin) are briefly treated. The authors' own work included studies of morphology, biochemical reactions, pathogenicity, antiserum production, agglutination tests and complement fixation. A survey of the flora of normal skin and mucosæ of 577 persons is the basis for a catalogue of the characters of saccharomyces, cryptococcus and monilia (endomyces were not met), as well as of some of the species. A useful plan for the identification of species was submitted as well as a key.

The studies were conducted under reliable auspices at the University of Illinois and appear to be careful and thorough. Probably the most important outcome was the opinion that a study of morphology and biochemical reactions can suffice for identification; agglutination tests, while dependable, are not necessary except with doubtful strains. Monilia albicans was not found on normal skin, but occurred in feces, in gastric contents, and in mucous membranes under normal conditions.

F. W.

BONES. A Study of the Development and Structure of the Vertebrate Skeleton. By P. D. F. MURRAY, M.A., D.Sc. Pp. 203; 45 illustrations. Cambridge: At the University Press; New York: The Macmillan Company, 1936. Price, $2.50.

THE author presents some new ideas and unpublished experiments. The main part of the book is in the first four chapters, where the author discusses the embryonic and postembryonic development, together with the structure of the skeleton in relation to its many functions. The language is so well chosen and simple that even a layman would not be mystified with unnecessary technical terms. This characteristic makes the book of special value to the young student interested in this field. There are also excellent photographs and clear, understandable diagrams. The concluding chapters are devoted mainly to the mechanism of bony adaptations and the conclusions drawn from these facts. Dr. Murray plainly states that he does not attempt to cover the field in its entirety or to be definite and final in his viewpoint; he hopes that his studies will help thrown some light on the rather obscure processes of bony development. T. O.

A TEXT-BOOK OF NEURO-ANATOMY. By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Pp. 519; 307 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $6.00.

THIS greatly expanded second edition shows many changes and additions and gives a well-balanced account of the structure of the nervous system from several points of view. There are 4 new chapters. These deal with the evolution and comparative anatomy of the nervous system (I), myelinization (VII), peripheral and central spinal conduction pathways (XI), and laboratory directions and clinical illustrations (XXVI). In the latter 14 clinical cases are briefly presented. At the end of each chapter a summary of the important points is given in a page or two. This addition will be welcomed by the student, and is of real value in crystallizing the subject. Over 100 illustrations have been added from many sources, and enhance the usefulness of the book. W. A.

NEW BOOKS.

Trauma and Disease. Edited by LEOPOLD BRAHDY, B.S., M.D., Physician in Charge of Industrial Diseases and Accidents in the Office of the Corporation Counsel of the City of New York, and SAMUEL KAHN, B.S., M.D., Medical Examiner in the Bureau of Workmen's Compensation of the Department of Labor, State of New York, New York City, with 25 Contributors. Pp. 613; illustrated. Philadelphia: Lea & Febiger, 1937. Price, $7.50.

The Thyroid and Its Diseases. By J. H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University, and Chief of the Medical Services, Massachusetts General Hospital. Being an Account Based in Large Measure on the Experience Gained in the Thyroid Clinic of the Massachusetts General Hospital by 14 Physicians and Surgeons and Many Other Collaborators, Past and Present. Pp. 602; 73 illustrations. Philadelphia: J. B. Lippincott Company, 1937. Price, $6.00.

Source Book of Orthopædics. By EDGAR M. BICK, M.A., M.D., Adjunct Orthopædic Surgeon, Hospital for Joint Diseases and Mt. Sinai Hospital; Attending Orthopædic Surgeon, Lutheran Hospital, etc. Pp. 376. Baltimore: The Williams & Wilkins Company, 1937. Price, $4.00.

The Avitaminoses. The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By WALTER H. EDDY, PH.D., Professor of Physiological Chemistry, Teachers College, Columbia University, etc., and GILBERT DALLDORF, M.D., Pathologist to the Grasslands and Northern Westchester Hospitals, Westchester County, N. Y. Pp. 338; 3 illustrations and 27 plates. Baltimore: The Williams & Wilkins Company, 1937. Price, $4.50.

Medical Urology. By IRVIN S. KOLL, B.S., M.D., F.A.C.S., Attending Urologist, Michael Reese Hospital. Pp. 431; 92 illustrations, 6 colored plates. St. Louis: The C. V. Mosby Company, 1937. Price, $5.00.

Yoga. A Scientific Evaluation. By KOVOOR T. BEHANAN, PH.D., Institute of Human Relations, Yale University. Pp. 270; illustrated. New York: The Macmillan Company, 1937. Price, $2.50.

The Spectacle of a Man. By JOHN COIGNARD. Pp. 252. New York: William Morrow & Co., Inc., 1937. Price, $2.50.

Contributions to the Microscopic Anatomy of the Pancreas by Paul Langerhans, [Berlin, 1869]. Reprint of the German original with an English Translation and an Introductory Essay by H. MORRISON, M.D. Pp. 39; illustrated. Baltimore: The Johns Hopkins Press, 1937. Price, $1.00.

The Cardiac Glycosides. A Series of Three Lectures Delivered in the College of The Pharmaceutical Society of Great Britain under the auspices of the University of London. By PROFESSOR ARTHUR STOLL, D.Sc., M.D. (HONORIS CAUSA), of Basle, Switzerland. Pp. 80; 24 illustrations (1 in color) and 11 tables. London: The Pharmaceutical Press, 1937.

Why We Do It. An Elementary Discussion of Human Conduct and Related Physiology. By EDWARD C. MASON, M.D., PH.D., F.A.C.P., Professor of Physiology, University of Oklahoma School of Medicine, Oklahoma City. Pp. 177; 5 figures. St. Louis: The C. V. Mosby Company, 1937. Price, $1.50.

A Summer Camp for Diabetic Children. Pp. 27. *New York Diabetes Association Annual Report for 1936.* Pp. 16. New York: New York Tuberculosis and Health Association, Inc., 1936.

Clinical Allergy. Due to Foods, Inhalants, Contactants, Fungi, Bacteria and Other Causes. Manifestations, Diagnosis and Treatment. By ALBERT H. ROWE, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco; Chief of the Clinic for Allergic Diseases of the Alameda County Health Center, Oakland, Calif., etc. Pp. 812. Philadelphia: Lea & Febiger, 1937. Price, $8.50.

Autopsy Diagnosis and Technique. A Manual for Medical Students, Practitioners, Pathologists and Coroners' Physicians. By OTTO SAPHIR, M.D., Chairman, Nelson Morris Institute for Medical Research; Pathologist, Michael Reese Hospital; Associate Professor of Pathology, University of Illinois Medical School, Chicago. Foreword by LUDWIG HEKTOEN, M.D. Pp. 342; 65 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, $5.00.

A Hundred Years of Medicine. By WYNDHAM E. B. LLOYD, M.A. (CANTAB.), M.R.C.S. (ENG.), D.P.H. (ENG.). Pp. 344. London: Gerald Duckworth & Co., Ltd., 1936. Price, 15/-.

The 1936 Year Book of General Medicine. Edited by GEORGE F. DICK, M.D., LAWRASON BROWN, M.D., GEORGE R. MINOT, M.D., S.D., F.R.C.P. (HON.) EDIN., WILLIAM B. CASTLE, M.D., AM., M.D. (HON.) Utrecht, WILLIAM D. STROUD, M.D., GEORGE B. EUSTERMAN, M.D. Pp. 848; 178 illustrations. Chicago: The Year Book Publishers, Inc., 1936. Price, $3.00.

Hemophilia. Clinical and Genetic Aspects. (Illinois Medical and Dental Monographs, Vol. I, No. 4). By CARROLL LA FLEUR BIRCH, M.D., Assistant Professor of Medicine. Pp. 151; 23 plates of illustrations, 11 figures, 3 tables and 75 charts. Urbana, Ill.: University of Illinois, 1937. Price, Paper bound, $2.00; Cloth bound, $2.50.

NEW EDITIONS.

Physiology in Health and Disease. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 1124; 191 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $9.00.

Synopsis of Pediatrics. By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine, and Pediatrician-in-Chief to the St. Mary's Group of Hospitals, etc. Assisted by T. S. ZAHORSKY, B.S., M.D., Instructor in Pediatrics, St. Louis University School of Medicine and Assistant Pediatrician to the St. Mary's Group of Hospitals. Pp. 367; 80 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1937. Price, $4.00.

A Laboratory Manual of Physiological Chemistry. By D. WRIGHT WILSON, Benjamin Rush Professor of Physiological Chemistry, University of Pennsylvania. Pp. 288. Third edition. Baltimore: The Williams & Wilkins Company, 1937. Price, $2.50.

"This laboratory manual of physiological chemistry is arranged for students familiar with elementary inorganic, theoretical and organic chemistry. It is intended to be used as a teaching manual and not as a comprehensive reference book. . . . As there is little variation in the type of material presented in various courses of physiological chemistry, we have found no difficulty in using this manual in our medical, dental and veterinary courses." (From Preface.)

A Medical Formulary. By E. QUIN THORNTON, M.D., Emeritus Professor of Therapeutics in the Jefferson Medical College, Philadelphia. Pp. 363. Fourteenth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $2.75.

"The United States Pharmacopœia which became official July 1, 1936, shows drastic revisions to which this edition conforms. Twenty-eight modern drugs, preparations and chemicals have been added to the list of official substances and thirty-five official Latin names and forty-six English titles have been changed." (From Author's Preface.)

The Essentials of Chemical Physiology. For the Use of Students. By the late W. D. HALLIBURTON, M.D., LL.D., F.R.S., Fellow of The Royal College of Physicians; Emeritus Professor of Physiology in King's College, London, J. A. HEWITT, PH.D., D.Sc., Senior Lecturer in Physiology, University of London, King's College, and W. ROBSON, PH.D., D.Sc., Reader in Biochemistry, University of London, King's College. Pp. 350; 56 illustrations, including 1 colored plate. Thirteenth edition. New York: Longmans, Green & Co., 1936. Price, $4.00.

The present edition, the first published after death of the original author, stresses the applications of biochemistry to physiology. It contains more didactic and explanatory matter than usually found but in works of this type the inclusion of discussions preserves the manual's readability. D. D.

Handbook of Microscopical Technique. For Workers in Animal and Plant Tissues. Edited by C. E. MCCLUNG, PH.D., Professor of Zoölogy, and Director, Zoölogical Laboratory, University of Pennsylvania. Thirty-four Contributors. Pp. 698; 82 illustrations. Second edition, revised and enlarged. New York: Paul B. Hoeber, Inc., 1937. Price, $8.00.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
FRANKLIN G. EBAUGH, M.D.
PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,
AND
GEORGE JOHNSON, M.D.
PROFESSOR OF NEUROPSYCHIATRY, LELAND STANFORD JUNIOR UNIVERSITY.

MEDICINAL THERAPY IN PSYCHIATRIC DISORDERS.

I. The Hematoporphyrin Treatment of Depressive Psychoses.

In the past few years several drugs of considerable interest have been introduced in the therapy of the psychoses. To name only a few, the treatment of morphine withdrawal symptoms with insulin, the use of insulin shock in the schizophrenic reactions, and the administration of benzedrine in affective disorders have been, and are at the present time, the object of intensive study. An historical survey of previous attempts to treat mental disorders by means of drugs must make even the most optimistic physician cautious in accepting enthusiastic reports without detailed and critical evaluation over a long period of time. Nevertheless, continuous therapeutic experimentation is indispensable in those psychiatric conditions in which our knowledge of etiology and our present methods of treatment are unsatisfactory. Although the study of the psychodynamics and psychologic mechanisms in the psychoses remains the focal point of interest for the psychiatrist, we welcome any method which may help us in treatment and at the same time may eventually clarify obscure etiologic problems. In the following, an important recent contribution in this field, the hematoporphyrin therapy of the depressions, will be reviewed.

The treatment of depressive psychoses with hematoporphyrin was inaugurated in 1930 by Hühnerfeld,[17b,c] following a series of animal experiments,[17a] in which he found that injections of small amounts of the substance resulted in gain of weight, overactive and aggressive behavior and increased response to external stimuli. Since depressions are characterized among other things by loss of weight, decreased psychomotor activity and lessened response to stimuli, Hühnerfeld regarded the drug as worthy of trial in human beings. By 1931 he was

able to report the results of treatment in 13 cases,[17c] of which 11 had shown marked improvement or recovery, while only two were unchanged. A series of publications by this author continued to report highly favorable results.[17d-j] By the end of 1935 Hühnerfeld had treated 90 cases of endogenous depression and involutional melancholia, all of them severe enough to require hospitalization; of these 48 recovered or were greatly improved, 30 were somewhat improved, and 12 were unaffected. The author believes that the consistently observed mode of recovery excludes the possibility of his having confused therapeutic effect with spontaneous improvement. The cases which responded to treatment showed, uniformly, first an improvement in the somatic-vegetative field (weight, turgor, sleep, etc.), and then a lessening of the mental symptoms, of which generalized inhibition (retardation) was usually the first to disappear. Moreover, clinical improvement in most cases was noted within 2 to 14 days after the treatment was instituted.

The treatment method, as recommended by Hühnerfeld, is of two types, oral and intramuscular. In mild cases the patient is given 10 drops of a 0.5% hematoporphyrin hydrochloride solution (oral "Photodyn") in water 3 times daily before meals. The dose is increased daily by 1 drop until it reaches 30 drops t.i.d., and then decreased at the same rate until the original level is reached, and treatment discontinued. Thus the usual duration of this type of treatment is 41 days, the total dosage somewhat less than 600 mg. In some cases the treatment is prolonged to 60 days with a dosage of 700 mg. When the psychosis is more severe, a 0.2% solution is injected intramuscularly, beginning with either ½ cc. or 1 cc., followed by 9 injections of 1 cc. every other day. After the tenth injection a rest period of 7 to 10 days is interposed, after which a series of 10 injections of 2 cc. on alternate days is given; the first of these is frequently reduced to 1 cc. This type of medication lasts 47 to 50 days, with a total dosage of 57 to 60 mg. It has subsequently been modified by Hühnerfeld, who in his latest publications[17i,j] recommends oral administration for mild and moderately severe forms of depression, and a combined oral and injection therapy for the very severe cases. In this latter method the patient is given small oral doses of hematoporphyrin, about 10 drops t.i.d., during the whole course of intramuscular injections, including the rest period, and thus receives about 300 mg. *per os* in addition to the 60 mg. injected.

The favorable results reported by Hühnerfeld soon led other clinicians to investigate the value of the method. In Germany, Italy, and France publications by André,[2] Becker,[6] Bianchini,[7] Cimbal,[10] Giehm,[13a] Hartmann and Weissmann,[15] Küppers,[22] Meyer,[27] Vinchon[41] and others reported results which, although in general not quite as favorable as those of Hühnerfeld, nevertheless indicated that hematoporphyrin was of marked therapeutic value in a large number of depressions. In this country Strecker, Palmer and Braceland[39a] were the first to undertake a study of this treatment, reporting in 1934 a series of 37 cases, of which 23 were manic-depressives, 8 involutional melancholias, and 6 schizophrenics. Excluding the latter, of the 31 depressives treated, 9 showed marked sustained clinical improvement, 7 moderate clinical improvement, 8 general physical improvement, while 7 remained unchanged. Their conclusions were that hematoporphyrin in some way

increases the available energy, and that actual somatic and psychic benefits seemed to be derived from its administration, especially in the affective disorders. In a second communication,[39b] the same authors report equally favorable results in 24 additional cases. Angus[3] administered hematoporphyrin to 41 cases of symptomatic depression of long standing, with an apparently poor natural prognosis. Included in this group were 15 manic-depressives, 11 involutional melancholias, 9 depressed schizophrenics, 3 depressed psychoneurotics, and 3 miscellaneous depressed states. Six of the manic-depressives improved greatly or recovered, 2 improved, 1 showed transitory improvement, and 6 were unchanged. The corresponding figures for the total group were 8, 10, 5 and 18. The author concludes that hematoporphyrin is of definite value in the treatment of depressions, including those of apparently malignant character. Most of the above mentioned authors agree with Hühnerfeld that it is possible to distinguish between the therapeutic effect of the drug and spontaneous improvement. Strecker, Palmer and Braceland list separately those cases in which they feel certain that the improvement was dependent upon the administration of hematoporphyrin, those in which this was highly probable but not certain, and those in which the evidence did not permit of a verdict one way or the other.

In contrast to the otherwise unanimously favorable opinion of those who have investigated the method, two publications report negative, or almost negative, results. Notkin *et al.*[29] treated 10 cases of involutional melancholia. One patient showed sustained improvement, 3 were moderately but only transiently improved, while the remaining 6 were unchanged. The same authors also experimented with hematoporphyrin therapy in 10 cases of schizophrenia, only 2 of which showed some depressive coloring; none of these patients improved. Steinberg[37] reported the results of treatment in 14 patients, comprising 8 manic-depressives, 5 involutional melancholias, and 1 undiagnosed psychosis. One manic-depressive showed sustained improvement, and another transient improvement; the remaining patients were not benefited. Hühnerfeld,[17b,j] commenting on Steinberg's results, states that in addition to the diagnostic uncertainty of some of the cases he regards the doses used as too small for such severe depressions. It is true that where combined oral and intramuscular administration was used by Steinberg, the patients received on the average only 100 to 150 mg. of hematoporphyrin by mouth in addition to the 60 mg. by injection; but it is hardly likely, in view of the immediate improvement with corresponding doses noted by other observers, that this alone would account for the negative results. On the other hand, some of the cases were unquestionably diagnostically uncertain, and, what is more important, the series was a small one.

The total results of hematoporphyrin therapy to date can be summarized as follows, taking into account only those publications which list the number of patients treated, and the degree of improvement noted: Of 423 patients treated, 351 belonged to the group of endogenous depressions and involutional melancholias; of these, 173 (49.3%) recovered or were greatly improved, 103 (29.4%) were moderately or slightly improved, and 75 (21.3%) were not helped at all. Of the 71 cases of involutional melancholia, slightly more than ⅓ failed to respond

to the treatment. Hühnerfeld, Giehm and Vinchon have observed that cases in which anxiety is a prominent feature are especially resistive to treatment. Hühnerfeld feels that exogenously conditioned (reactive) depressions are not amenable to this form of therapy unless endogenous factors also are present; and, in common with Schwarz, stresses the need for differential diagnostic studies in order to obtain more precise indications for the treatment. Angus[3] believes that the main indication for the use of hematoporphyrin lies in the presence of symptomatic depression rather than in the minute diagnosis. Pending further large scale investigations, the evidence at present is greatly in favor of the assumption that hematoporphyrin exerts a markedly beneficial effect on many depressive patients, particularly in the endogenous (manic-depressive) group.

The dangers involved in the treatment appear to be minimal. Hühnerfeld considers it certain, on the basis of his experimental and clinical studies, that the doses recommended by him exclude the possibility of any serious toxic manifestations. Hutschenreuter[18] found that 20 times the maximal oral dose used in treatment was well tolerated by rats, although postmortem microscopic examinations revealed fatty degeneration of the liver, hyperemia of the splenic pulp, and some hemosiderosis. The usual intramuscular dose produced some toxic effects, but in his opinion the difference in body weight between human beings and the experimental animals should allow for a wide margin of safety. To date no deleterious toxic effects have been noted, with the exception of a few unpleasant but harmless erythemas (Strecker *et al.*,[39a] Tieke,[40]) and 1 case of photophobia (Strecker *et al.*); one of the erythemas reported by Strecker *et al.* resulted from a nurse injecting the drug subcutaneously instead of intramuscularly. Steinberg[37] felt that in some of his cases the drug was definitely harmful from the psychiatric point of view, but noted no injurious toxic reactions. As regards somatic contraindications, Hühnerfeld limits these to organic affections of the liver and severe acute febrile disease. He has treated patients with pulmonary tuberculosis, nephrosis, arteriosclerosis and myodegeneration of the heart, and has observed no harmful effects. In all cases of organic illness, however, he restricts himself to the oral administration of the drug, and in very advanced arteriosclerosis reduces the dose to half the usual amount.

The encouraging results reported above, and the possibility that through further study of the method something may be learned as to an underlying metabolic disturbance accompanying or causing true endogenous depressions, have naturally aroused great interest in the mode of action of hematoporphyrin in these conditions.

The chemistry and physiology of the porphyrins can be discussed only briefly in this review. For an excellent presentation of the rôle of these substances in human pathology the reader is referred to Mason, Courville and Ziskind,[24] where he will find the literature cited in detail. Of even greater importance is the general biologic significance of the porphyrins, particularly as regards their chemistry, in which field great advances have recently been made. They are widely distributed in the plant and animal kingdom, being closely related to many of the major biologic pigments. Hematoporphyrin is derived from hemin (acid heme) by the splitting off of iron; heme being one of the two com-

ponents of hemoglobin. Phylloporphyrin, a magnesium-free derivative of chlorophyll, and hematoporphyrin, an iron-free derivative of hemoglobin, can both be reduced to the same substance, hemopyrrol. Cytochrome, an intracellular pigment found in aërobic bacteria, yeast, higher plants, and animals, is a derivative of heme, being composed of three hemochromogen-like compounds, cytochrome a, b, and c. Cytochrome c, when subjected to HBr-glacial-acetic-acid degradation, yields a crystalline hematoporphyrin. Egg-shells contain oöporphyrin, an isomer of protoporphyrin, traces of which are found normally in all human organs, in the feathers of some birds, in the sprouts of plants and elsewhere. The yeast cell can synthesize coproporphyrin, found physiologically in small quantities in feces, urine, milk, bile and meconium, and pathologically in larger amounts in the serum, urine and feces of indviduals with congenital hematoporphyria, as well as in plumbism, pernicious anemia and other diseases. Uroporphyrin is also found physiologically in normal urine, and in large amounts in all types of hematoporphyria. The copper salt of this compound, turacin, has been isolated from the feathers of the turaco, a South African bird. These examples should suffice to illustrate the prevalence of these substances, and their importance in animal and plant physiology. Nevertheless, the assumption of earlier workers that hematoporphyrin was synthesized in the liver, and took part in the formation of hemoglobin, has not been substantiated by subsequent investigations, which have failed to produce any evidence that hematoporphyrin occurs in normal intermediary metabolism. The porphyrins found in the urine of healthy individuals as well as those seen in cases of so-called "hematoporphyria" (better "porphyria") are uroporphyrin, coproporphyrin, and occasionally other natural porphyrins, but not hematoporphyrin. Recent experiments to determine whether orally or parenterally administered hematoporphyrin is partly converted into one or more of the natural porphyrins were inconclusive, but pointed to a negative result (Hutschenreuter[18]). Structurally, the various porphyrins differ from one another chiefly in the number of carboxyl groups in the molecule. Through decarboxylization of any of them, etioporphyrin, consisting of four substituted pyrrol rings, may be obtained. Although all the known porphyrins and many of their isomers have been synthesized, some question as to their structural formulas still exists. Hematoporphyrin, which contains two carboxyl and two hydroxyl groups, has the formula $C_{34}H_{38}O_6N_4$, but recent studies indicate that there may be only 33 carbon atoms instead of 34.

Two physicochemical properties common to all the porphyrins are fluorescence and the production of photosensitivity, which are closely related to one another. Photosensitivity in man was first described by Bazin[5] in discussing the pathogenesis of hydroa vacciniforme. Anderson[1] reported the presence of porphyrins in the urine of patients with hydroa aestivale. The first actual demonstration of the photodynamic action of a drug, however, was made by Raab[33] in 1898, when he found that acridine solutions would kill paramecia much more quickly when exposed to light, although light alone had no deleterious effect on the organisms. Following this discovery much work was done on the phenomenon of photodynamic action, which has retained the interest of investigators up to the present time. For a discussion of the

nature of the photochemical processes involved, the reader is referred to the publications of Blum.[8]

The investigation of the photosensitizing effects of the porphyrins, particularly of hematoporphyrin, was undertaken by Hausmann.[16] This author first proved that a strong solution of hematoporphyrin was fatal to paramecia, and demonstrated that under corresponding conditions erythrocytes were destroyed. He studied the effects of graduated doses of the drug on white mice, distinguishing four degrees of photosensitization according to the dose given and the intensity of irradiation. 1, In *light stroke* the animal first becomes restless, scratching the ears, nose, and other parts of the body violently. The pulse and respiration rate increase, and the skin becomes livid. Then the animal becomes comatose, the blood pressure falls, and death occurs. 2, In the *acute photodynamic reaction* the blood pressure first rises, accompanied by tachycardia and paroxysmal hyperpnea. A pronounced erythema appears over the entire body. Later the blood pressure falls rapidly, and the animal dies unless protected from light. 3, In *subacute photosensitivity* only erythema and edema of the skin are found. 4, In *chronic photosensitivity*, when the dose is still smaller, and the exposure to light brief but repeated, the animal's ears become necrotic, and hair falls out in a ring-shaped area around the eyes. These experiments have been repeated and expanded by various investigators in the attempt to explain the symptoms found. Pfeiffer[31] performed an interesting experiment on parabiotic white rats, in which only one of the pair was exposed to light, but the other died subsequent to the irradiation, frequently before the irradiated partner. Smetana,[36] however, in a similar experiment with parabiotic mice found that only the one exposed to light was injured. Rask and Howell,[34] working with dogs, concluded that death was caused by vascular collapse, and demonstrated that the low blood pressure was due to paralysis of the cutaneous circulation and not to a toxic effect of the drug or of skin toxins on the central nervous system. Awoki[4] found that white mice sensitized with hematoporphyrin and then narcotized with urethane did not show the usual motor excitation, but nevertheless died in the same length of time as unnarcotized mice when irradiated. This same author showed that serum injections will protect white mice against the fatal effects of hematoporphyrin sensitization. The experiments of Hühnerfeld and Hutschenreuter with small doses of the drug have already been mentioned. Strecker, Palmer and Braceland[39b] studied the behavior of white rats following graded intraperitoneal injections of photodyn, the commercial hematoporphyrin used in the treatment of depressions. Rat 1, used as a control, received no hematoporphyrin, but was exposed to ultraviolet radiation, during which he appeared much more active and interested; 30 minutes later he was active, eating and drinking; after 12 hours his behavior was normal. Rat 2 received 0.6 mg. of hematoporphyrin. Before exposure to ultraviolet light his behavior was normal; during exposure he was markedly hyperactive, and was even more active 30 minutes later, scratching himself, washing his face frequently, and apparently suffering from some irritation of the skin; 12 hours later he appeared normal. Rat 3, receiving 1.2 mg., was unchanged before irradiation, but during exposure appeared ill, was uninterested, and showed photophobia; after 30 minutes he was more

active than 1 or 2, and suffered marked skin irritation; 12 hours later he was still overstimulated, racing about. Rat 4 was given 1.8 mg. and showed no change before exposure to ultraviolet irradiation; during exposure he seemed definitely ill, with marked photophobia, sluggishness and inactivity; 30 minutes later he still was inactive and suffering from photophobia; after 12 hours he was extremely active and overstimulated, racing about his cage and climbing up the wire; the irritation of the skin was still present.

There have been comparatively few experimental investigations of the photodynamic action of hematoporphyrin in human beings. Meyer-Betz[28] experimented on himself with an intravenous injection of 0.2 gm., and suffered for weeks with extreme dermal photosensitivity. He observed that light which passed through a window pane was apparently no less injurious than direct sunlight. Strauch[38] administered 0.12 gm. intravenously to 3 rachitic children; all of them developed erythema and edema of the skin with subsequent ulceration and necrosis. Duke[12] showed that intradermal injections of small amounts of porphyrin caused local dermal sensitivity to light. Blum, in a personal communication to Strecker, Palmer and Braceland[39b] reports the results of interdermal injections of photodyn in humans. The injection of 0.1 cc. of a 0.01% solution (0.01 mg.), followed by exposure to bright sunlight for 2 or 3 minutes, resulted in the formation of an extensive itching wheal surrounded by spreading erythema. The wheal subsided after 1 to 2 hours, and was succeeded later by pigmentation. Of particular interest was the fact that the removal of oxygen from the tissue by occlusion of the circulation prevented the formation of the wheal and the erythema. With a 0.004% solution it was very difficult to obtain any definite photosensitizing effect. Ohta[30] undertook studies of the blood and urine of hematoporphyrinized rabbits, using medium sized doses. The animals who were exposed to sunlight showed a decrease in hemoglobin and the number of erythrocytes, and an increase in fats and fibrinogen. Within the limits of the experiment no definite changes in blood sugar, carbon dioxide, total nitrogen and non-protein nitrogen could be elicited. A second group of animals, who were also given hematoporphyrin but were kept in the dark for a week, showed no appreciable blood changes. The urine was examined before and after sensitization; the values for creatinine, uric acid, urea, ammonia, total nitrogen, chlorides, calcium and magnesium were found to be unaffected.

Studies to determine the relative powers of photosensitization of the various porphyrins have been carried out by Schumm,[35] Dankmeyer[11] and Grzeschiuchna[14] among others, and have shown that the commonest prophyrins may be graded as to photodynamic potency in the following order: hematoporphyrin, uroporphyrin, deuteroporphyrin, coproporphyrin, and protoporphyrin, the first named having 20 times the photosensitizing effect of the last.

The question as to what type of light has the strongest effects on hematoporphyrin-sensitized organisms is of considerable theoretical interest (*cf.* Blum[8b]), and may prove of practical importance in the therapy under discussion. In common with the natural porphyrins, hematoporphyrin shows maximal absorption in the visible region of the spectrum around 560 mμ (yellow light), with a second peak at about 400 mμ

(violet and long wave ultraviolet). Kögel[21] recently studied the sensitivity of hematoporphyrin in the concentration used by Hühnerfeld, and found that it was sensitive to the whole of the visible spectrum as well as to some infra-red and ultraviolet rays, but chiefly to yellow light. He concluded that ultraviolet irradiation, such as has been used by the majority of workers, can be of no particular advantage in hematoporphyrin therapy.

Boyd[9] has made an interesting study of hematoporphyrin from a different point of view. Following the observation of Howell that hematoporphyrin and light were capable of changing fibrinogen into a more soluble form of protein, Boyd investigated this phenomenon to discover whether actual hydrolysis of the protein took place, and whether the reaction could be considered an enzymatic one. He found that four factors were necessary for the hydrolytic reaction: molecular oxygen, hematoporphyrin, water, and radiant energy. His theory of what actually takes place in this process may be summarized as follows: Hematoporphyrin unites with the protein in a salt compound. Through the absorption of light the energy of the hematoporphyrin molecule is increased. Molecular oxygen then unites with the hematoporphyrin molecule, and oxidizes it. Through this the energy content of the hematoporphyrin is increased to the point that it becomes unstable and decomposes, at the same time giving some of its energy to the protein with which it is united. The energized protein molecule then unites with water, and is hydrolyzed.

If, after this necessarily brief survey of the chemical, physical and biologic aspects of hematoporphyrin, we return to the question of how the drug acts when therapeutically administered to depressed patients, we find no explanation that is entirely satisfactory. Hühnerfeld's original hypothesis was that through skin sensitization stimuli were transmitted to the vegetative centers, thus exerting a favorable action in the "volitional and sensory spheres." In his more recent papers[17i,j] he distinguishes 3 modes of action of hematoporphyrin: 1, a photodynamic effect on the vegetative centers; 2, a stimulative-tonic effect, manifested by improved appetite, increased weight, increased turgor of the skin, and, where secondary anemia is present, an improvement in the blood picture; and 3, a vegetative-regulatory effect, as shown by increased salivation, lessening of gastro-intestinal and vasomotor disturbances, and by the reported influence of the drug on the electrolyte balance, on the blood-sugar level, and on the hydrogen-ion concentration of the urine. The theory of the transmission of stimuli from the photosensitized skin to vegetative centers, with a resultant release of inhibitions, is, as Hühnerfeld himself points out, merely a working hypothesis. As such it is accepted by the majority of European workers in this field, but it is wholly without experimental foundation, and at the present is not capable of being either proven or disproven. The laboratory data concerned with the postulated stimulative-tonic and vegetative-regulatory effects of hematoporphyrin will be reviewed below.

Boyd, in a personal communication to Strecker *et al.*,[39b] mentions two possibilities as to the action of hematoporphyrin. He quotes Zeile and Hellstrom to the effect that liver catalase contains an iron-porphyrin complex, and points out that cytochrome is known to contain

hemin. In view of these facts he suggests that hematoporphyrin may act as a respiratory catalyst, promoting a greater cellular respiration. Boyd's second theory, based on his investigation quoted above, is that following the reaction of hematoporphyrin with tissue proteins, highly reactive chemical substances may be split off, thus producing a stimulating effect on the organism, possibly in the form of a mild anaphylactic shock. Blum, in another personal communication to Strecker, Palmer and Braceland,[39b] suggests that increased cellular respiration may be one of the major factors at work, and cites the demonstration by Wohlgemuth and Szörenyi that the oxygen intake of cells is increased by hematoporphyrin even in the dark, and to a much greater extent when light is present. It should be pointed out, however, that Wohlgemuth and Szörenyi[42] believe this increased use of oxygen to be quite different from ordinary cellular respiration, in that it is dependent neither upon the structure of the cell nor to a great degree upon temperature. The theories of increased cellular respiration and of protein shock rest on a firmer experimental foundation than does Hühnerfeld's hypothesis of the transmission of stimuli to the vegetative nervous system through skin sensitization; yet both need further clarification before they can be accepted as even partial solutions of the problem. There can be no doubt but that the concept that hematoporphyrin plus light increases cellular respiration is of fundamental importance for further research in this field. Strecker, Palmer and Braceland suggest the possibility that this action may account directly for the therapeutic effect, citing the work of McFarland[25] on the psychological effects of oxygen deprivation; but it must be said that in general anoxemia results in toxic-delirious and occasionally schizophrenic-like symptoms, rather than in depressive ones. As regards the direct therapeutic effect of protein shock, there is no reliable clinical or experimental evidence that endogenous depressions are greatly influenced by shock effects; on the contrary, these conditions are characterized by a course which, more than in any other psychosis, appears to be independent of accidental somatic or mental stimuli, such as intercurrent febrile disease and psychic traumata. Only a few examples to the contrary are reported in the literature (Pilcz[32]). Menninger[26] stated that only 2 cases of postinfluenzal recovery from depression were recorded in the literature up to 1930; Levin[23] has recently reported another. Furthermore, the clinical and laboratory data to date present no evidence that an anaphylactic-like shock, even a mild one, occurs in the usual course of treatment. Nevertheless, it would be worth while to test this theory by a carefully controlled series of depressives treated with protein shock therapy. As far as is known to the reviewer, foreign protein shock is one of the few forms of medication that has not, at one time or another, been tried in depressions. Autohemotherapy was recently studied by Giehm,[13b] who obtained good results in reactive depressions (probably suggestive), but very poor ones in the endogenous group.

The data relative to the "stimulative-tonic" and "vegetative-regulatory" effects of hematoporphyrin can be summarized as follows:

Body Weight. Hühnerfeld[17d] observed that 3 pigs, when given oral doses of hematoporphyrin in amounts which corresponded ac-

cording to weight with the usual treatment doses in humans, gained 40 to 50 pounds more than other pigs from the same litter, although receiving the usual nourishment. Clinically, he finds that in most cases the body weight increases, often rapidly, but gives no further information. Of the 37 patients treated by Strecker, Palmer and Braceland in their first series, 20 gained in weight, the average increase being 5½ pounds, 10 patients lost weight, 3 of them being under weight reducing programs; and 7 patients showed no change in weight at the end of the treatment, although several of these had gained considerably at some time during the treatment. Angus[3] found no appreciable change in those cases which improved, but a moderate gain in weight in the unimproved cases. Of the 20 patients treated by Notkin *et al.*,[29] 12 showed a gain in weight, and 8 a loss. The 3 cases which were temporarily improved gained, whereas the patient with sustained improvement lost 6 pounds, which were later regained. Steinberg[37] reported gain in weight in 1 of his 14 patients, loss of weight in 1, and slight loss of weight in 2; in the other 10 cases no mention is made of gain or loss.

Basal Metabolism. Angus found that the basal metabolism in cases improving under hematoporphyrin therapy tended to rise, while in the unimproved cases there was a slight decrease. These findings, however, were based on averages for the two groups; the individual findings were not consistent enough to permit of any definite conclusion. Notkin *et al.* obtained basal metabolic readings in 14 cases before, during and after treatment; in 9 of these there was an increase during treatment, in 2 no change, in 3 a decrease. The findings after completion of the therapy were inconclusive. In 1 case of involutional melancholia showing temporary improvement there was a slight increase during and after treatment; in the other 2 temporarily improved cases, and in the 1 showing sustained improvement, no readings were obtained. Strecker *et al.*, in 12 cases, found no consistent pattern, and chiefly negligible changes.

Hemoglobin and Red Count. Hühnerfeld[17i] found in an unstated number of patients that "there was an almost consistent marked increase in the red count and hemoglobin, particularly in cases with secondary anemia," and feels that this observation to a certain extent confirms the old and subsequently discarded theory that hematoporphyrin takes part in the formation of hemoglobin. In their first series, Strecker *et al.* examined the blood of 16 patients, of whom 9 showed substantial increases in red blood cell count and hemoglobin, 1 was unchanged, and 6 showed moderate reduction. In their second series the same authors found slightly higher erythrocyte counts (100,000 to 250,000) in 8 cases, and slightly decreased counts (30,000 to 70,000) in 2. These are scarcely beyond the limits of biologic and technical variation. The accompanying hemoglobin changes were negligible, as were the variations in the white cell count. In the remaining 2 cases of the 12 examined the changes were greater. One patient with a moderate secondary anemia (Case 11) showed an increase of 740,000 cells, combined with a marked rise in hemoglobin; the other (Case 4) showed a decrease of 740,000 with no marked change in hemoglobin. Steinberg found the erythrocyte count lowered in 4 of the 5 cases examined; in one of these the decrease amounted to 1,350,000 cells.

Notkin *et al.* found increases of from 150,000 to 1,500,000 cells in 15 of the 19 cases examined; the average increase was 643,000. Angus observed an increase in hemoglobin and red count in most of his improved cases, but noted that in the unimproved group a distinct fall in both factors was the rule rather than the exception, and raised the question whether this may in the future prove to be a danger point in the therapy. In view of repeated experimental evidence that large doses of hematoporphyrin followed by irradiation can cause hemolysis of the erythrocytes, this warning is timely, and should lead to regular and frequent counts on all patients undergoing treatment. Detailed hematologic investigations of the effect of varying amounts of hematoporphyrin on animals and humans would be of great interest. At present, it appears that the drug, in a majority of cases, increases the number of erythrocytes when administered in small doses; the effect on the hemoglobin content is much less certain.

Blood Sugar. Küppers[22] found that hematoporphyrin lowered the blood sugars of his patients, particularly when some hyperglycemia was present before treatment. Although various reports on high blood sugars in depressions have appeared to the literature, Katzenelbogen and Friedman-Buchman[20] have shown that in general the values in these conditions are within normal limits. These authors, however, in common with several other investigators, found that the *sugar tolerance curve* in depressions shows a higher peak and a more prolonged decrement than otherwise. In general, the curve becomes normal with recovery from the illness. Angus made careful studies on the effect of hematoporphyrin on the sugar-tolerance curves, with the following findings: 1, The blood sugar was within normal limits before and after treatment. 2, The blood sugar fell during treatment. 3, The sugar-tolerance curves became more normal after treatment, not only in the improved cases, but to a lesser degree in many of the unimproved ones. This latter finding seems particularly significant insofar as it demonstrates that hematoporphyrin, even in cases in which no clinical improvement is noted, can produce laboratory findings which are usually associated with recovery. Steinberg, who examined blood sugars before and after treatment, but not during it, found no consistent changes. His values before treatment were extremely low; in the only case with a sugar level above 100 (105.26), the reading after treatment was 79. The same author investigated the *blood cholesterol* of 6 patients, and found a decrease following treatment in all of them.

Electrolyte Balance. Irrespective of whether or not the blood calcium level in depressions is raised, as is claimed by many investigators, or within normal limits (Katzenelbogen and Goldsmith[19]), the question as to the action of hematoporphyrin on the calcium-potassium balance is of great interest. Hühnerfeld[17c] found that hematoporphyrin reduced the calcium values in patients with hypercalcemia. Later,[17d] in experiments with pigs, chosen because their blood calcium level is similar to that of humans, he was able through the administration of doses comparable to those used in hematoporphyrin therapy to reduce the blood calcium of the three animals by 2.5 to 3 mg. %. The calcium level was lowest at the time when the largest doses were given, and returned to normal 4 weeks after the medication was terminated. Küppers and Vinchon[41a,c] confirmed these results clinically. The former

author in particular emphasized the importance of these findings, and expanded on them, claiming that in favorable cases the potassium level is raised concomitantly with the decrease in calcium and blood sugar, thus forming an important prognostic guide. Vinchon[41b] mentions in connection with the electrolyte balance his observation that the pH of the urine is lowered by hematoporphyrin. In 1 patient studied by Strecker *et al.* in their first series, the calcium values were 11.8 and 11.5 mg.% before treatment, 9.6 mg.% during treatment, and 10 mg.% afterwards. In their second series, 12 patients were examined and showed on the whole a slight increase. No correlations with improvement were attempted. Angus found varying decreases in both improved and unimproved cases, somewhat larger in the former; exceptions occurred in both groups, however. Steinberg's series shows 5 decreases as against 2 increases, but some of the changes were negligible. In this connection a factor should be mentioned which has not been taken into account by any of the investigators, and which may well play a rôle in obscuring the experimental results. Ultraviolet light, which has been used in varying amounts by different workers with hematoporphyrin, can, through radiation of ergosterol with resultant vitamin D formation, raise the calcium level of the blood; accordingly, the effects of hematoporphyrin on blood calcium can be evaluated only in cases not exposed to large amounts of ultraviolet.

It is apparent that, whatever may be the final judgment as to the therapeutic efficacy of hematoporphyrin treatment, it offers at the present time an unusual opportunity for combined biochemical, general medical and psychiatric research. Further progress will, it is felt, depend to a large extent on the degree to which laboratory findings can be correlated with the results of careful and persistent clinical psychiatric examinations.

JOHN D. BENJAMIN, M.D.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

JOSEPH C. BECK, M.D.,

ASSOCIATE PROFESSOR EMERITUS, DEPARTMENT OF OTO-LARYNGOLOGY, UNIVERSITY OF ILLINOIS MEDICAL SCHOOL,

AND

M. REESE GUTTMAN, M.D.

ASSISTANT CLINICAL PROFESSOR, DEPARTMENT OF OTO-LARYNGOLOGY, LOYOLA UNIVERSITY MEDICAL SCHOOL.

RECENT ADVANCES IN THE TONSILLAR ASPECTS OF SYSTEMIC DISORDERS.

THAT the tonsils continue to be a topic of interest to the otolaryngologist, as well as to the internist and general practitioner, is evidenced by the large number of contributions appearing upon the subject in recent years. While no spectacular discoveries that might profoundly affect our previous conceptions have been reported, there is a large number of interesting papers that serve to clarify our knowledge of tonsillar disease, especially as they relate to the complications incident to tonsillar infection and establishing more definite indications for their removal. There is an unmistakable trend away from the indiscriminate wholesale removal of the tonsils for various more or less vague reasons. Indications are becoming more precise and undoubtedly there is an increasing aversion from the so-called "slaughter of the innocents" unless the indication be placed upon a firm clinico-pathologic basis.

Pathology. That grossly pathologic tonsils which upon microscopic examination show varying evidence of chronic inflammation may frequently be attended with little or no clinical phenomena is a matter of common knowledge. Mueller[37] finds that the clinical and anatomic picture but rarely agree; many histologically pathologic tonsils manifesting few if any clinical symptoms. Even the purulent-appearing cryptic contents obtained by tonsillar expression are but rarely true pus; but, as Krompecher and Nemai[30] find, are exfoliated epithelial

cells that have undergone fatty degeneration and have as an admixture a varying number of neutrophils, lymphocytes, plasma cells, macrophages and bacteria. Smith[57] compared the clinical history and the histopathologic findings in a group of 104 tonsillectomies. Of the 45 cases that were operated upon because of repeated sore throats and colds, 87% showed histologic evidence of chronic inflammation, while 13% were normal. Of the 17 patients operated upon because of discharging ears, 59% evidenced infection and 41% did not. Those operated upon because of a possible focus of infection showed microscopic evidence in 86%. In a similar attempt to correlate the relation of the pathologic picture of a tonsil with the clinical cause for its removal, Jason[23] found that patients with systemic or distant changes showed greater tonsillar changes than those with purely local pharyngeal complaints. Hunnicut, Sternstein and McMahon,[21] in a study of 25 tonsillectomies, were unable to find any histologic change that was definitely related to either the clinical signs and symptoms or the bacterial flora. The pathologic findings were similar to those found in a control group. Even normal-appearing tonsillar fossæ may harbor infective organisms after tonsillectomy, is a conclusion of Solis-Cohen,[58] after finding the same pathogenic organism both before and after tonsillectomy. Should this be substantiated, the possible cause of many failures of improvement of systemic disorders following removal of the tonsils is obvious. In the study of the tonsils as a possible focus of infection in systemic disorders, Nissen[43a] found that the gross lesions were of 4 types, namely, acutely inflamed tonsils with or without suppuration; chronically, reddened hypertrophic tonsils with or without symptoms; a tonsil in which the anterior pillar or soft palate is purplish red in color, and the presence of infected pharyngeal follicles. Tilley[61] also believes that a purplish-red discoloration of the anterior pillar signifies a pathologic tonsil, especially if the tonsillar gland is enlarged and there is an abundance of pus extruded from the tonsillar crypts that contain a preponderance of leukocytes upon microscopic examination.

Cardiac Disease. In consideration of the question of the optimal time for tonsillectomy in the presence of a complicating endocarditis, Zimányi[68] calls attention to the many untoward results that are encountered if the operation is performed at a time in which the defensive mechanism of the body is at low ebb. He believes that the patient is in an optimal condition for operation when his defensive mechanism is most efficient and in a positive phase that can be shown by determining the bacteriologic index which normally is between 50 and 55. Tonsillectomy should, therefore, be performed only at a time in which the bacteriologic index is normal in order to avert any possible disastrous complication. A bacteriologic index below normal should be a contraindication to operation.

It is to be admitted that tonsillectomy is frequently of benefit in endocarditis; Curtius, Dieker and Wirth[10] observed in 41 tonsillectomies that existing cardiac conditions frequently improve after the procedure, although an exacerbation may be noted if decompensation has been present. Of the 23 patients that survived to the reëxamination time, 13 showed disappearance of the cardiac symptoms. There was little, if any, benefit if the operation was performed in a period in which there

existed a febrile florid endocarditis, and the authors properly concluded that the operation should only be performed during an afebrile period. In 8 patients with an endocarditis lenta no effect on the fatal course was noted.

Holtz and Friedman[19] described a red eruption on the oral and pharyngeal mucosa that occurred in association with cases of rheumatic endocarditis. They were small pinpoint to 2 mm. circular, crimson to bluish, non-elevated lesions. They appeared in recurring crops lasting about 24 hours. The authors believed the eruption to be a non-embolic hemorrhagic exanthem.

Rheumatic Fever. There has been continued interest in the relation between tonsillar disease and arthritis and rheumatic fever. Kaiser[25] finds that while sore throat was the preceding infection in 59% of his 1200 rheumatic children, the recurrent attacks were not lessened in tonsillectomized children. The mortality rate was 50% less in children who had their tonsils removed, and the incidence of rheumatic infection was slightly more in children whose tonsils were not removed at the initial attack. In a study of histologic serial sections of the neck organs, Sarafoff[51] was unable to find any typical changes in the tonsils and adenoids in several cases of rheumatic fever. On the contrary, the peritonsillar tissues disclosed evidence of rheumatic disease in 4 of 7 cases. Evidence of non-specific infection were found throughout the pharynx, indicating that in all probability the tonsils were not the sole portal of entry. In similar studies, Klinge[27] found serial sections of the tonsils in 2 patients that revealed similar evidence of rheumatic infection in the peritonsillar structures. In 5 other patients with a similar history, no specific rheumatic findings in the peritonsillar tissues were noted. In a study of the blood in rheumatic patients that had acute streptococcic pharyngeal infection, Schlesinger and Signey[52] could demonstrate the presence of streptococcic precipitins, which corresponded to the type of organism responsible for the infection. Their appearance usually foreshadowed an attack of acute rheumatism, and the authors believe that immediate therapy instituted promptly would prevent serious relapses, although they concede that it is not infallible.

In a discussion of the part played by the tonsils and adenoids in the etiology of rheumatic fever, Coates and Gordon[8] emphasize the importance of lymphoid remains, hypertrophied lateral pharyngeal bands and isolated lymphoid follicles on the posterior pharyngeal wall.

Blood Dyscrasias. There appears to be further concern with the pharyngeal lesions associated with blood dyscrasias. Jones[24] properly points out that the presenting symptom in many blood dyscrasias is a marked throat manifestation that the patient not infrequently consults an otolaryngologist, who must be aware of such a possibility and be prepared to perform the ordinary simple laboratory tests in every suspected case. A description of the early pharyngeal lesions in 3 cases of agranulocytosis by Costen[9] calls attention to the frequency with which the anterior pillars are involved. The lesions represent a necrotic process on the surface of the tonsil or a mere solution of the tissues involved. All 3 cases gave a history of prolonged drug ingestion which the author believes is evidence of the profound depression of the bone marrow function caused by certain medicaments. Larsen[32] points out that some believe agranulocytosis to be a real clinical entity provoked

by some unknown factor, while others regard it as the expression of a disturbed leukopoietic system as a sequel of a general infection. Another theory is that the clinical findings are an expression of a state of low general resistance following a disturbance originating in the bone marrow. He describes his case as one of secondary development, caused by infection with toxic effects on the bone marrow. Gangrenous tonsillitis may be an expression of an acute lymphatic leukemia. Nagasawa[40] reports a case of a child of 4, who had a swelling and redness of one tonsil and the neighboring palate. The upper pole of the tonsil was necrotic; there was anemia and glandular swelling. Microscopic examination of the blood disclosed acute lymphatic leukemia, with death in 1 week. Richter[49] presented 2 cases of acute sore throat attended with a constant lymphocytosis, with a normal or slightly subnormal total number of leukocytes. The lymphocytosis persisted after the acute infection had subsided. He investigated several close members of the respective families and found a similar lymphocytosis present, and so concluded that the phenomenon was a constitutional and familial characteristic. The clinical aspects of infectious mononucleosis was presented by McKinley[34] in a study of 50 patients over a period of 12 years. He advocates the term "infectious mononucleosis" in order to avoid such nondescript terms as "glandular fever." The most constant feature was the cervical lymphadenopathy, which may persist for some time and does not suppurate. Marked glandular enlargement was observed in individuals with but minimal pharyngeal findings. Pharyngeal findings varied from slight faucial injection to swelling of the lymphoid tissue and infrequent membrane formation. There was a variable total leukocytosis up to 30,000. There was a relative and absolute lymphocytosis present at some time in the course of the disease. There were no characteristic bacteriologic findings in the pharynx and blood cultures were repeatedly negative. There was no demonstrable effect on the injection of emulsion of fresh glandular substance into guinea pigs and monkeys. It would appear that the constancy of the lymphadenopathy would suggest that the offending etiologic factor and the primary lesion reside in the lymph nodes. There has been further interest in the serologic diagnosis of infectious mononucleosis made by testing the blood serum for the presence of heterophilic antibodies. This new phase in the diagnosis of this disorder was initiated in 1932 by Paul and Bunnell[44] when they found that the blood serum in such patients was able to clump sheep red cells in high dilutions, which normally occurs only in decidedly low dilutions. Davidsohn and Walker[12] and Stuart and others[59] reported on the nature of the heterophilic antibodies found in infectious mononucleosis. Bernstein[4] showed that this disorder may be simulated by some 29 conditions and that the value of the test is apparent, and Davidsohn[11a] enumerates several others. In another contribution on the subject, Davidsohn[11b] concludes that the test is of decided confirmatory value in typical cases, and of diagnostic importance in the differential diagnosis of conditions that may simulate it.

Nephritis. In an extensive review of the subject of the bacteriologic aspects of peritonsillar phlegmon, Guiffrida[13] reports that a transitory albuminuria could be observed in 37% of all cases of peritonsillar suppuration, a true parenchymatous nephritis being observed in 2%. Of the 37% complicated by renal involvement, streptococci were the

offending organisms in 20% and pneumococci in 13%. In a discussion of the value of tonsillectomy in children, Nadoleczny[39] concludes that acute glomerular nephritis and embolic focal nephritis without nephrosclerosis are frequently improved by tonsillectomy, while chronic nephritis is unaffected by it. deWesselow, Goadby and Derry[65] investigated the urinary findings in 354 patients with tonsillitis. There was present an early albuminuria in some 15% of the patients and a late albuminuria in 6%. From the clinical and urinary findings a focal nephritis was probably present in 10% and a diffuse glomerulo-nephritis in 0.8%. There was apparently no relation to the presence of hemolytic streptococci in the pharynx and the incidence of the focal nephritis.

Arthritis. In a study of 500 patients with arthritis, Nissen[43a] noted that 90% had their tonsils intact before the onset of the joint symptoms. In addition to the usual pathologic tonsil, Nissen believes that infected lymphoid tissue in the nasopharynx is a greater focus of infection than is usually realized. In another contribution[43b] he stresses the importance in determining three important factors that associate arthritis with tonsillar disease, namely, the recognition of obvious or concealed infection in nasopharyngeal tissue, recognition of the involvement of the joints and other systemic effects, and determination of the association between the two. These are carried out by careful, prolonged and intensive study of the patient. In a discourse on the treatment of 438 patients with rheumatism who had tonsillectomy performed, he found that 300 were entirely symptom free, 100 showed varying degrees of improvement and in 38 no benefit was noted.

Endocrines. An endocrine rôle has frequently been attributed to the tonsils. Peller[45] in a large statistical study, in comparing the state of the tonsils and the constitutional attributes, concludes that they act as inhibitors to growth, weight, height and rate. This action is apparently unaffected by the presence of chronic infection. He believes the tonsils to be definite endocrine organs. He finds that tonsillectomized girls menstruate and mature earlier than average girls. Blonde girls he finds present tonsillar hypertrophy and are consequently more often tonsillectomized than brunettes. He concludes that further research is necessary to explain these and other relationships. In another contribution in association with Zimmerman,[46] he finds that the tonsils inhibit puberal development of the mammary glands, as tonsillectomized girls show earlier mammary maturation. Halasz[14] believes that the tonsils are endocrine glands and that a deficiency in their internal secretion aids in the formation of ozena. He states that this disagreeable affliction may be benefited by subcutaneous injection of tonsillar extract in addition to extracts of the closely related thymus and thyroid glands.

Pulmonary Suppuration. The question of post-tonsillectomic lung infection continues to receive interest. Waldapfel[64a] is unable to explain the relatively large number of pulmonary complications seen in this country in comparison to the relatively infrequent reports from Germany. He believes that it might be due to the superficial anesthesia, retention of the pharyngeal reflexes and use of the upright position. In 8 cases of post-tonsillectomic pulmonary complications he found that fever and roentgenography were most important in arriving at a diagnosis. The prognosis in his cases was good. Schutz[55] describes the various pulmonary complications following tonsillectomy and finds

they are not serious as a rule and clear up quite rapidly. He reviews the theories of formation and finds that of aspiration is untenable, as it is practically impossible to produce pulmonary abscess in animals by injecting blood and pus into the bronchi. Injections of infected material into the jugular vein on the other hand produced septic pulmonary infarcts. As with most German writers, he attributes the large number of such complications reported in this country to the use of deep general anesthesia. Ranson and McGolrick,[48] in reporting a case that recovered following operation, briefly discussed the manner of production and the treatment.

Tuberculosis. In discussing the tonsil as a portal of entry in tuberculosis, Schlittler[53b] reviews 98 cases of chronic cervical lymphadenopathy but in whom no evidence of tuberculosis of the lung or other portions of the body could be discovered. Histologic examination of the tonsils removed in these individuals disclosed tuberculosis in 48. Only one tonsil and consequently only one-sided cervical enlargement was noted in 73% of the cases. Schlittler believes that the localization of the lymphadenopathy to the glands at the angle of the jaw draining the tonsils, the absence of tuberculous disease in other portions of the body and the relative frequency of unilateral involvement and the discovery of microscopic evidence of tuberculosis in such a high percentage of the excised tonsil all speak for the tonsils being the seat of a primary tuberculosis. In another contribution on the subject,[53a] he stresses the presence of a subacute and chronic lymphadenitis of the angle of the jaw as a diagnostic sign of primary tonsillar tuberculosis. In a study of 112 tuberculous adults, Newhart, Cohen and Van Winkle[42] found tuberculous tonsils in 42%. They also find that the tuberculous lesion is rarely a gross one, only being found at microscopic examination. This is in agreement with Schlittler's findings noted above. In addition, it was observed that in some instances in which routine sections were reported as normal, serial sections revealed tuberculous foci. There were no primary lesions noted in their cases, all being secondary to the open pulmonary lesion and resulting from constant contact with the bacillus-laden sputum. They conclude that tonsillectomy presents no special hazard when proper precautions are taken in tuberculous individuals. Hudson and Wollaston[20] cite a case of massive tuberculosis of the tonsils which gave a history of repeated attacks of sore throat over a period of 2 years. They conclude from the clinical course and from the histopathologic findings in the tonsils that the primary focus of the tuberculous infection was in the tonsils.

Syphilis. Sore throat and tonsillitis are relatively common findings in early syphilis. These persist for some time with few constitutional symptoms. In a study of 803 patients with early secondary syphilis, Brittingham[5] found subjective sore throat and objective tonsillitis in about 29%. Of 502 patients with secondary syphilis, tonsillar lesions were observed in about 25%. In 301 patients with ultra secondary disease, tonsillar changes were noted in some 35%. It is apparent that routine serologic tests must be employed in all cases of pharyngeal involvement without systemic manifestations that persist for more than a week. In a study of the tonsillar tissues of 139 syphilitic patients macerated and subjected to dark-field illumination, Kumasawa[31] was able to find the spirochete in 3 of 13 patients with primary lesions and

in 18 of 27 patients with secondary lesions. In later stages of the disease the spirochete could be observed even in individuals in whom the Wassermann reaction was negative. Pund and Brawner[47] described the histopathologic findings in 2 cases of syphilitic tonsillitis. They were characterized by a diffuse fibroblastic and angioblastic proliferation with large mononuclear cells in the lymphatic stroma. There was, in addition, foci of epithelioid cells in the neighborhood of the crypts. Mainzer[35] reports 2 cases of syphilitis of the tonsil. Chancre of the tonsil is unilateral, as a rule coming on with a sore throat, enlargement of the tonsil, and eventually swelling of the regional lymph glands.

Tonsillogenic Septicemia. In a survey of tonsillogenic sepsis, Haymann[16] found an incidence of 5.3 per 1000 in a review of 12,500 necropsy reports. In some 30% of the cases the tonsils could not be grossly identified as the origin of the sepsis, and in about 35% peritonsillar or retropharyngeal abscess was present. He suggested that the sepsis could originate by direct entrance of the causative organism into the blood stream, from isolated thromboses of the retrotonsillar veins, by indirect entrance *via* the lymphatic channels and by secondary venous thrombophlebitis from parapharyngeal phlegmon. Waldapfel[64b] differentiates two types of sepsis: *via* retrograde thrombophlebitis and by means of the lymphatics and lymphadenitis and secondary involvement of the cervical vein. He also stresses the fact that the primary portal of entry, the tonsil, is not always the focus of sepsis which is most often in the parapharyngeal space, and that appropriate therapy must take this fact into account. He therefore opens the neck in every suspicious case in order to drain the parapharyngeal space and to examine the jugular vein. He also removes the tonsil if local gross changes are present. The clinical manifestations indicating such a procedure are symptoms of general sepsis, associated with chills and the finding of tenderness and infiltration along the course of the jugular vein. He stresses the jugular glands as septic foci and insists on their removal when inflamed. Beck[2] discusses the diagnosis and treatment of parapharyngeal infections and jugular thrombosis, emphasizing the tonsils as the point of origin and indicating surgical drainage of the neck and resection of the jugular vein. Uffenorde[63] reports several cases illustrating the pathway from the infected tonsils to the lymphatics and the lymph glands and then involvement of the jugular and facial veins. He advocated enucleation of the tonsils, opening of the vascular sheath in the neck, removal of the inflamed glands, inspection of the veins of the neck and their resection if thrombotic and opening of the parapharyngeal space. Myers[38] reports 3 cases of post-tonsillitic pyemia with septic metastases in various portions of the body. In a discussion of postanginal sepsis, Abt[1] reports 4 cases in children and stresses the grave prognosis. He concluded that the earlier the responsible focus is detected and evacuated the better the prognosis. The similarity of postanginal septicemia to puerperal sepsis is discussed by Schneider.[54] Both diseases spread by vascular, lymphatic and perivascular phlegmon routes. They both may eventuate into pyemia with secondary suppuration in the joints, kidneys, lung and heart. The therapy is comparable in both disturbances, the elimination of the primary locus, the evacuation of suppurative collections, the ligation and resection of veins in the presence of endophlebitic extension. Both are extremely

grave diseases with a fatal outlook in about 50%. Hybasek[22] reports several cases of sepsis following angina and tonsillectomy and concludes that drainage in sepsis is more important than tonsillectomy. Peritonsillar abscesses should be evacuated and drained, but tonsillectomy is contraindicated in peritonsillar phlegmon. He believes that there is little need for prophylactic ligation of the jugular, but advises ligature and resection of all thrombotic vessels. There must be thorough incision and drainage of the neck and parapharyngeal space. In contradistinction to the occurrence of sepsis following tonsillitis, Krauspe[29] presents clinical and experimental evidence that tonsillitis may at times be a sequel to a blood stream infection. Histologic examination of the tonsils in a number of individuals who died of a variety of acute infections disclosed inflammatory reactions which were interpreted as being hematogenous in origin. There were many abscesses and focal areas of necrosis. Bacteria, especially the streptococcus, could be demonstrated in the subepithelial capillaries. Kolbe[28] was able to demonstrate hematogenous metastases in the tonsils in 1 of 16 cases of general sepsis. He believes that the tonsils are infrequently so affected as they appear to possess a certain immunity.

Scarlet Fever and Diphtheria. The effect of tonsillectomy on the development of immunity was studied by means of the Dick test by Kereszturi and Park,[26] who were unable to note any marked effect in changing a positive Dick reaction to a negative one. Buice[6] subjected a number of children to the Schick test and found the proportion that gave a positive reaction to be about the same in both, namely 62% in tonsillectomized children and 69% in those with intact tonsils. In a comparison of the course of scarlet fever and diphtheria which occurred before and after tonsillectomy in several thousand cases, von Zsindely[70b] found a decreased incidence of both after tonsillectomy, but also noted the decreased incidence declined with the elapsed time following operation. In another communication, von Zsindely[70a] observed that the percentage of diphtheria carriers were higher in the presence of enlarged tonsils and adenoids.

The Question of Tonsillectomy for Peritonsillar Abscess in the Acute Stage. In the past decade there have been increasingly more contributions advocating the performance of tonsillectomy in the acute stage of a peritonsillar abscess. While many feel that such a procedure is without danger, there are many theoretical objections which are obvious and that may find support in practice. In a discussion of 90 patients upon whom tonsillectomy had been performed for peritonsillar abscess, Zollner[69a] reports several complications including a temperature rise to 104.8° F. with chill, and also a phlegmonous infiltration in the base of the tongue. He notes that patients in whom only simple incision is performed had an immediate drop in temperature more often than those tonsillectomized, and that postoperative febrile episodes were more common in the tonsillectomized than in the incised patients. He concludes that incision is the procedure of choice in early peritonsillar abscess and in those cases in which the abscess is well localized. Tonsillectomy should be reserved for those cases in which no pus is obtained and in which fever persists after simple incision and when there are signs of sepsis. In another contribution[69b] he reports 4 fatal cases in 91 patients tonsillectomized for peritonsillar abscess. All died of septi-

cemia in spite of relatively good pre-operative conditions of the patients. He finds simple incision adequate in most cases and finds indication for tonsillectomy in the three states noted above, namely, delayed recovery following simple incision, failure to recover pus on incision, and in the presence of sepsis. In review of 356 cases of peritonsillar abscess including 29 of his own, Tato[60] concludes that tonsillectomy affords a quick, safe, cure, eliminating the possibility of recurrence. He had but two complications: a postoperative hemorrhage and 1 case of sepsis with rheumatism. Hofer and Motloch[18] review 30 patients with peritonsillar abscess treated by tonsillectomy. They noted a prompt drop in the temperature with but one exception. They believe that tonsillectomy in this condition is free from danger and is the operation of choice. In a series of 542 patients with peritonsillar abscess, Tonndorf[62] found that 99% showed adequate relief by simple incision through the anterior pillar. He believes that while tonsillectomy is not as serious as might be expected, its indication is present only in sepsis and in which healing fails to occur after simple incision. A comparison of simple incision, incision and secondary tonsillectomy, and tonsillectomy in the acute stage of the disease by Linck,[33] causes him to conclude that simple incision at times does not evacuate all the pus and that recurrences and relapses are common. Incision and secondary tonsillectomy has the advantage that complications are avoided by the removal of the tonsil. However, the disadvantage of the multiple operation and the possibility that a recurrence or relapse might occur before the secondary operation, lead the author to conclude that immediate tonsillectomy is the operation of choice for both immediate cure and prophylaxis against future difficulty. Advantages that are claimed are that there is not peritonsillar collection of pus that cannot be evacuated by this method, recurrences are impossible as no abscess cavity can exist after tonsillectomy. The author minimizes the danger that might be expected in operating upon acutely inflamed tissue and upon decidedly sick patients. Canuyt[7] has had experience with many tonsillectomies in peritonsillar abscess, but considers it painful and at times dangerous. Neither does he believe in waiting for long periods of time for removal of the tonsil until marked postinflammatory adhesions are formed which may make the future procedure difficult and also run the danger of a recurrence during the interval. He advocates waiting for a period of 4 or 5 days after the simple incision preferably after the temperature has dropped to normal or nearly normal. He believes that at this time the operation can be safely, easily performed under local anesthesia.

The Value of Surgical Diathermy in the Treatment of Chronic Tonsillitis. Surgical diathermy or the use of electrocoagulation in the removal of tonsils at one time had reached the status of a fad with the laity as well as with some members of the profession itself. There arose a tremendous demand on the part of the public for this method of surgery out of all proportion to its merits. Fantastic claims as to simplicity of operation and lack of pain or bleeding have all proven untrue in actual practice. We have repeatedly, by the spoken as well as the written[3] word, opposed the fallacious claims for a period of some 10 years. The recent literature on the whole is decidedly antagonistic to the method, and in all probability it is now going the way of most

medical fads. We have been impressed with but one indication for its use, namely, in the removal of tonsillar tags and lymphoid hypertrophy remaining after orthodox surgery. The present status of this method is well presented by Roberts,[50] who finds that the tonsil is not and in all probability may not be entirely removed by surgical diathermy. Secondary hemorrhage is not uncommon and postoperative pain is present as with the orthodox operation. In addition, infection and edema are quite frequent and in many cases the incomplete removal by diathermy may necessitate surgery subsequently. Mock,[36] in a similar vein, states that when the public learns of the dangers and complications incident to this method and especially of the possibility of leaving a buried focus of infection behind, it will undoubtedly shun it. In a report on their experience with the method, Shambaugh and his associates[56] find that it is not painless and that secondary hemorrhage can occur, and there is uncertainty as to the total removal of the tonsil. Finally Yonker,[67] in a thorough review of the subject, concludes that the results are unsatisfactory, and expresses his doubts as to any indication for its use.

Roentgen Ray Therapy of Chronic Tonsillitis. There has been a renewed interest in the Roentgen ray treatment of chronic tonsillitis. In a report on 32 patients that were followed up out of 47 treated by this method, Hasenjager[15] believed there was a cure in 23, improvement in 5 and no benefit in 4. He believes it can be used in all cases in which surgery is contraindicated with the exception of children under 2 years. Hess[17] reported a cure in 68% of his 31 cases. He believes that the benefit was due to the destruction of the lymphoid cells. In some 54 children with recurrent attacks of tonsillo-adenoiditis, Niemeyer[41] was enabled to observe a freedom from recurrence for over 2 years in about two-thirds of the cases and a milder attack in the remaining third. However, one scientific investigation seems to throw some doubt as to the validity of these admittedly clinical deductions—22 young men were subjected to irradiation of one of their tonsils, with proper protection to the other by Wolff.[66] Histologic examination of both tonsils removed later revealed no noteworthy difference between the irradiated and non-irradiated tonsil.

M. REESE GUTTMAN, M.D.

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PHYSIOLOGY

PROCEEDINGS OF

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The Chemotropic Attraction of Leukocytes by Fraction of Streptococcus Hemolyticus. H. M. Dixon, Morton McCutcheon, and E. J. Czarnetzky (Laboratories of Pathology and Bacteriology, University of Pennsylvania). Previous studies have shown that the chemotropic attraction of neutrophils to bacteria *in vitro* is brought about chiefly by substances given off by the bacteria. The present

experiments represent an initial step in identifying such substances, by testing the chemotropic effect *in vitro* of certain fractions of *Strep. hemolyticus.** These fractions were: (1) A labile antigen consisting of a protein-carbohydrate complex, which, on injection into rabbits, produces specific agglutinating and phagocytosis-promoting antibodies; (2) a protein-free, non-antigenic, crystalline, stable hemolysin; (3) a carbohydrate (fairly pure and freed of protein). Each of these 3 substances was adsorbed on kaolin (which by itself does not attract leukocytes) and was then tested as a source of attraction for rabbit neutrophils *in vitro*. The leukocytes were obtained by injecting physiologic saline solution into the peritoneal cavity; the exudate was mixed with plasma, and a drop of the mixture was allowed to spread between slide and coverslip, with the coated kaolin particles in the center. Under the microscope, it was observed that leukocytes were strongly attracted to the particles coated with the labile antigen, but not to those coated with the other 2 fractions. It is concluded that of the 3 fractions of hemolytic streptococcus tested, the one which calls forth phagocytosis-promoting antibodies is also the substance that attracts leukocytes to the bacteria, thus making possible their phagocytosis.

A Chemotactic Substance Derived From Epithelium. DANIEL SILVERMAN (Laboratory of Pathology, Jefferson Medical College). Studies on chemotaxis were made by direct observation of leukocytic behavior according to McCutcheon's technique. Normal human skin, mechanically pulped without contact with water, showed strong chemotropism, a coefficient of +0.83. The chemotropic substance was dissolved out of pulped skin by extracting in hot water; skin pulp so treated showed no chemotaxis—a coefficient of +0.05. Chemotropism was demonstrated in the extract by evaporating the latter and soaking the previously extracted pulp in the concentrate. On testing this, a coefficient of +0.77 was obtained. The extract gave positive reactions for protein and free amino acid, but negative reactions for carbohydrate and histamine. A solution of histamine phosphate, tested in the same manner as the watery extract of skin, showed only slight chemotropic property—a coefficient of +0.25. Our results with preparations of *Staph. aureus* (coefficient +0.61) compared favorably with McCutcheon's results.

It is concluded that normal human skin contains an actively chemotropic substance (or substances), which is water-soluble and thermostable and which may be responsible for the behavior of leukocytes in inflammation following non-infected injuries. In infected areas the chemotaxis may depend in part on bacterial substances and in part on substances derived from the injured tissues.

The Synthesis of Octopine (Pectenine). J. LOGAN IRVIN and D. WRIGHT WILSON (Laboratory of Physiological Chemistry, University of Pennsylvania). Two years ago Drs. Moore and Wilson reported before this Society the isolation from scallop muscle of a compound which they later named pectenine. The description of properties given

* For the method of preparation of these fractions see Mudd, S., Czarnetzky, E. J., Pettit, H., and Lackman, D.: Labile Bacterial Antigens and Methods for Their Preparation and Preservation, Proc. Am. Philos. Soc., in press.

by Moore and Wilson, similar in most respects with that presented by Morizawa in 1927 for octopine, differed in that they had found that their free compound formed a neutral solution in water while Morizawa reported that his material was strongly alkaline. Recently Mayeda has shown that octopine monopicrate gives an acid reaction to Congo red which is in agreement with the observation of Moore and Wilson upon pectenine and indicates that Morizawa was in error. We therefore believe our compound to be octopine.

The structure of octopine was studied by Moore and Wilson who concluded that the compound is probably arginine, the α-amino group of which is joined to the α-carbon atom or propionic acid. In order to confirm this structure, we have carried out a synthesis involving a reaction between d-arginine and d, l-α-bromopropionic acid. Comparisons were made between the synthetic and natural materials in the free state and in the form of two salts. The results indicate that partially inactive octopine was synthesized. We plan to treat d-arginine with optically active bromopropionic acid in order to obtain the naturally occurring isomer.

Observations on the Effect of Adrenalectomy on the Hypertension Produced by Kaolin. W. A. JEFFERS, M. A. LINDAUER, and F. D. W. LUKENS (Robinette Foundation, Cox Institute, and Pepper Laboratory, University of Pennsylvania). Arterial hypertension was produced in 9 dogs. Four of these survived the removal of both adrenal glands. One animal exhibited a fall in blood pressure to normal following the second adrenalectomy. This fall was interpreted as being a remission from the effect of kaolin, since 3 other dogs showed a persistent hypertension after bilateral adrenalectomy as long as adrenal insufficiency was averted.

These experiments appear to confirm the negative rôle of the adrenal medulla in the maintenance of hypertension from kaolin. The cortical extract seemed to function merely to avert adrenal insufficiency, thus allowing the mechanism of hypertension to operate.

The Effect of Duodenal Stimulation in Man Upon Alimentary and Adrenalin Hyperglycemia. HARRY SHAY, J. GERSHON-COHEN, and SAMUEL S. FELS (Samuel S. Fels Research Fund and the Gastrointestinal Division, Medical Service I, Mt. Sinai Hospital). From an attempt to study glucose absorption in the human stomach by our method* of producing pyloric closure through duodenal stimulation, we were led to consideration of the problem embodied in the title. The data we obtained indicate that: (1) Glucose, at least in high concentration, may be absorbed by the human stomach; (2) duodenal stimulation by hydrochloric acid will prevent a rise in blood sugar even though the amounts of sugar absorbed would ordinarily raise the blood sugar level; (3) the same effect was observed in a diabetic patient but did not occur in a very severe diabetic with a calcified pancreas; (4) the prevention or counteraction of alimentary hyperglycemia by duodenal stimulation is shown to be not a function solely of hydrochloric

* Shay, H., and Gershon-Cohen, J.: Experimental Studies in Gastric Physiology in Man: II. A Study of Pyloric Control: The Rôles of Acid and Alkali, Surg., Gynec. and Obst., **58**, 935, 1934.

acid. Other agents which could stimulate the duodenal mucosa were equally efficacious. Thus similar results were obtained with fat, hypertonic solutions or sodium chloride and sodium bicarbonate, and of glucose itself; (5) while duodenal stimulation could prevent alimentary hyperglycemia, peculiarly enough, it did not carry the depression of glucose concentration below the fasting level. These observations are similar to those of Laughton and Macallum who found that their duodenal extract did not reduce the blood sugar below the normal resting level after induced hyperglycemia; (6) duodenal stimulation did not alter the normal fasting blood sugar level; (7) duodenal stimulation failed to prevent or decrease the hyperglycemia incident to adrenalin injection.

From a study of the literature on the effect of duodenal extracts and their possible method of action, we believe there is adequate evidence to show that their action is not due to secretin or to an insulin extract from the duodenum. It would appear to depend, in the dog, upon a combination of islet stimulation and direct action of a duodenal hormone upon glucose metabolism. From the results reported in the depancreatized animal, the direct action is the essential one. From our data in severe diabetes, it would seem that, in man, the duodenal mechanism is essentially concerned with islet stimulation. It would seem, therefore, that little could be expected from the use of duodenal extracts in the treatment of diabetes in man. In the mild cases of diabetes some effect from islet stimulation; in the severe diabetics probably no effect or even an injurious one by stimulation of already severely damaged islets.

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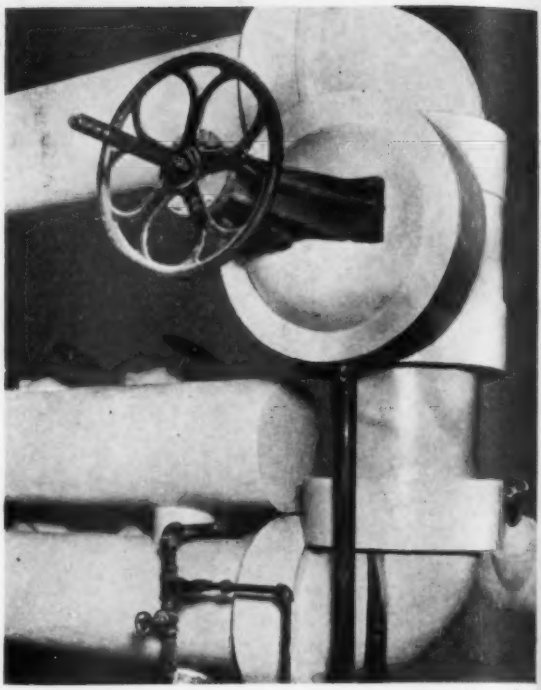

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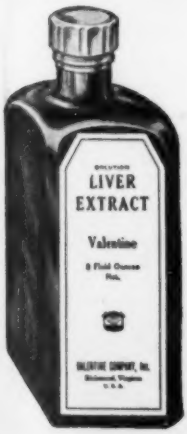

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